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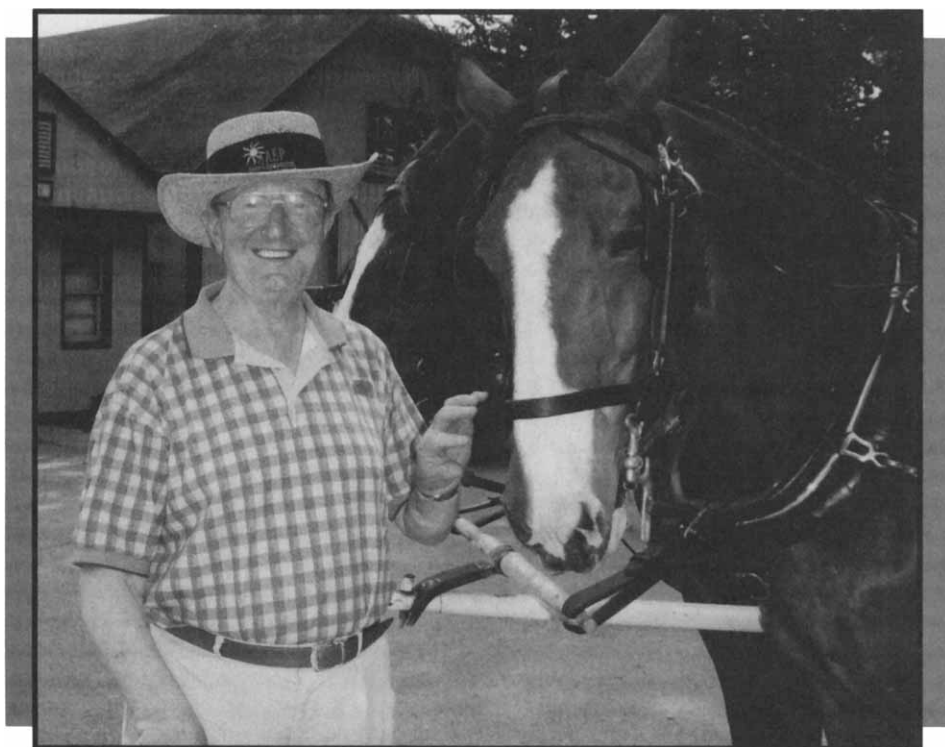
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*To my father, Norman Robinson, whose interest in horses  
began with Shetland ponies and timber wagons in his childhood  
and who—in his 90th year—is still just as keen on horses.*



# PREFACE

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**I**t has been 20 years since publication of the first edition of *Current Therapy in Equine Medicine*. When I told a colleague that I was preparing the first edition, he asked me how I would be able to continue producing new editions because there were so few equine specialists to advance the field and produce a fresh book every 4 or 5 years. This fifth edition attests to how wrong he was. The number of equine specialists has grown, and the technology that supports their diagnostic and therapeutic endeavors has evolved to a level that we could not even have imagined 20 years ago.

This growth of knowledge proves challenging in an attempt to compile a comprehensive text in less than 1000 pages. Clearly, it is not possible to be totally comprehensive, and therefore we have chosen to emphasize certain topics and cover others in less depth. It is my hope that by using the two most recent editions of the book, practitioners can find the information that they need to diagnose and treat most conditions of the horse. In this edition, we have devoted considerable space to the developing specialty of clinical pharmacology; provided a comprehensive section on infectious diseases; delved into gastrointestinal, skin, cardiovascular, foal, and eye diseases in considerable depth; and provided a detailed coverage of reproduction.

As usual, we have tried to emphasize the practical aspects of diagnosis and treatment and have provided details for therapeutic regimens. The reasoning behind this

approach is that *Current Therapy in Equine Medicine* is a book for the equine practitioner and for the student of equine medicine. I have great admiration for my colleagues who have the courage to be general practitioners because they are expected to answer questions on all aspects of horse medicine. I hope this book helps them to accomplish their task.

As usual, my role in production of this book is largely that of a conductor who tries to keep the sections of the orchestra working together to provide a coordinated whole. I relied on section editors to decide on the content of each section, to select authors, and to provide initial review of the chapters. To them and to the authors, I am extremely grateful, and I hope that they will forgive me if sometimes I nagged them at inconvenient times. I am also very thankful to Bill Gates and his ilk—who allow me to sit in one place and send manuscripts and photos around the world, check the accuracy of reference citations, locate the addresses of companies, and communicate with authors. This is quite a change from the way I did the first edition—when an entire room of my basement was taken over by stacks of paper, and I employed hourly labor to check information. Finally, I want to thank Kristen Mandava and Kristin Hebbard at Elsevier Science for their cheerful and helpful support. This has truly been a team effort.

**N. Edward Robinson**



**Color Plate 1** A scene as viewed by humans.



**Color Plate 2** The same scene as in Color Plate 1 corrected for equine visual acuity and color perception.



**Color Plate 3** A melting corneal ulcer (keratomalacia) resulting from infection with *Pseudomonas aeruginosa*.



**Color Plate 4** Photomicrograph of a cytologic preparation from a corneal ulcer showing fungal hyphae.



**Color Plate 5** Stromal abscess with iris prolapse.



**Color Plate 6** Clinical signs of acute equine recurrent uveitis (ERU). This horse has the "classic" form of ERU. An episode of acute uveitis, or flare-up, is evident with periocular swelling, epiphora, mucoid ocular discharge, blepharospasm, and corneal edema.

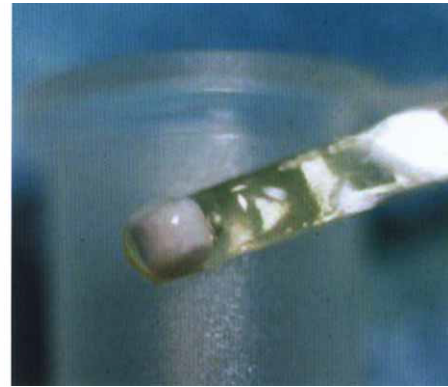


**Color Plate 7** Clinical signs of acute recurrent uveitis (ERU). Photograph of an eye with typical signs of acute-onset ERU. Clinical signs include periocular swelling, hyperemic conjunctiva, diffuse corneal edema, hypopyon, and a miotic pupil.

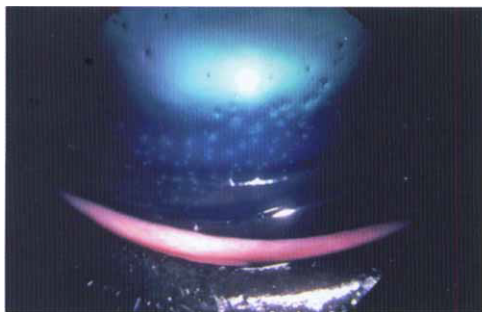




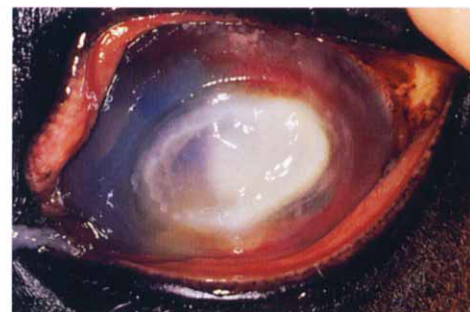
**Color Plate 8** Clinical signs of chronic equine recurrent uveitis. Multiple recurrent episodes of uveitis have resulted in phthisis bulbi, atrophy of the corpora nigra, posterior synechia, and cataract formation.



**Color Plate 9** Cyclosporine A intravitreal implant device.



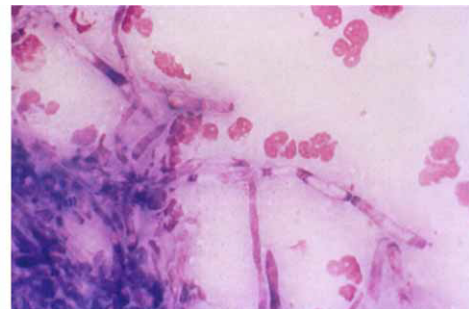
**Color Plate 10** Retroillumination clearly demonstrates multiple small, superficial corneal opacities on the cornea of a horse. The opacities retained fluorescein sodium dye but were more obvious when viewed by retroillumination. These opacities typify the clinical appearance of equine herpesvirus 2 (EHV-2) keratitis. (Courtesy Dr. David T. Ramsey, East Lansing, Mich.)



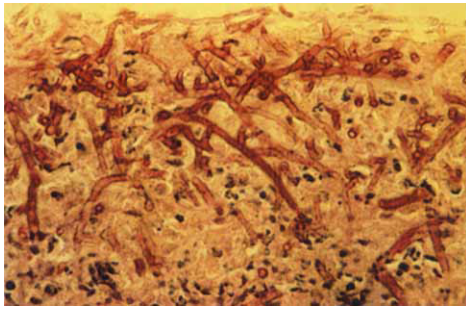
**Color Plate 11** Photograph of the eye of a 20-year-old Arabian with a long-standing fungal ulcer. The ulcer has raised, roughened edges and appears yellow-green. Numerous "satellite" lesions (fungal microabscesses) are evident near the periphery of the ulcer. Prominent corneal vasculature is also evident, and the pupil cannot be seen.



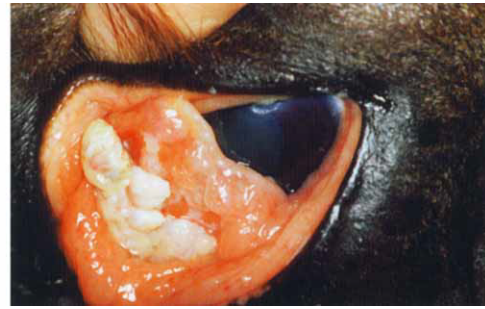
**Color Plate 12** Photograph of the eye of a 6-year-old American Quarter Horse with a deep stromal abscess in the central, left cornea. Note the presence of hypopyon in the ventral anterior chamber, diffuse corneal edema, and superficial corneal neovascularization. Fluorescein sodium dye has been applied to the cornea, and there is no stain uptake.



**Color Plate 13** Corneal cytology specimen obtained from a 2-year-old Thoroughbred horse with superficial fungal keratitis. The slide has been stained with Gomori methenamine silver, which causes the fungal hyphae to be seen as black elements.



**Color Plate 14** A standing keratectomy specimen from a Thoroughbred yearling with a melting corneal ulcer. The sample is stained with hematoxylin and eosin, and multiple fungal hyphae can be seen in the superficial stroma.



**Color Plate 15** Typical clinical appearance of squamous cell carcinoma (SCC) at this location. Proliferative mass of the nictitans with inspissated surface exudate.



**Color Plate 16** Typical clinical appearance of squamous cell carcinoma (SCC) at this location. A SCC at the lateral limbus, infiltrating the cornea.



**Color Plate 17** Typical clinical appearance of squamous cell carcinoma (SCC) at this location. Inflammation of a SCC of the lower eyelid near the medial canthus, 1 week after 5-fluorouracil (5-FU) injection.

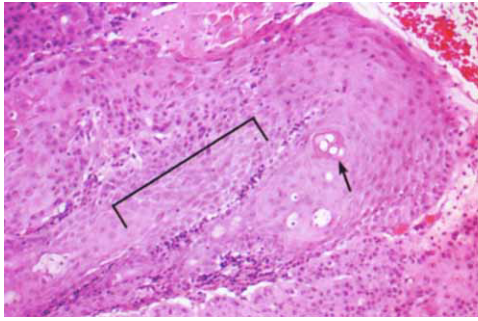


**Color Plate 18** Typical clinical appearance of squamous cell carcinoma (SCC) at this location. The same horse in Color Plate 17 1 year later. The mass near the medial canthus resolved after 5-fluorouracil (5-FU) injections; however, a new mass occurred in the middle of the lid 1 year later.



**Color Plate 19** Syringe and stopcock method of suspending 5-fluorouracil (5-FU) in sesame oil before intratumoral injection. Sesame oil is filtered before mixing.





**Color Plate 20** Photomicrograph depicting the histologic appearance of squamous cell carcinoma (SCC). Whorls of epithelial cells with multiple, prominent nucleoli surround central regions of keratin pearly (*arrow*). A region of prominent intracellular bridging is also apparent (*bar*). The image is an H&E stain, 42× magnification.



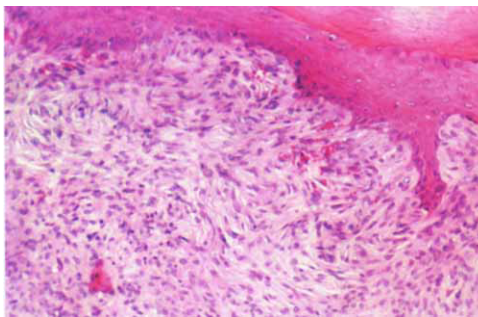
**Color Plate 21** Typical clinical appearance of a multilobular fibroblastic periocular sarcoid in a 4-year-old American Quarter Horse. Notice the alopecia and hyperkeratosis.



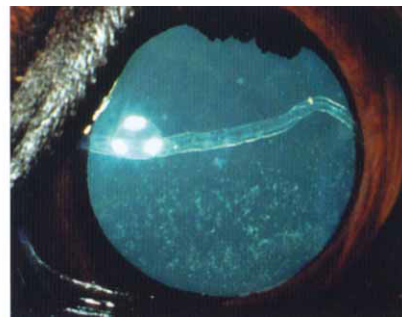
**Color Plate 22** Complete regression and cosmetic healing are evident 3 months after completion of intralesional *Bacillus Calmette-Guérin* (BCG) treatment.



**Color Plate 23** Typical clinical appearance of a verrucous sarcoid. The lesion is flat, thickened, and nodular.



**Color Plate 24** Photomicrograph depicting the histologic appearance of a sarcoid. Hyperkeratosis is evident at the top of the picture, with whorls of spindloid cells beneath the epidermis.



**Color Plate 25** Linear opacities at the level of Descemet's membrane are often found in cases of early glaucoma in the horse.

**Color Plate 26** Bilateral corneal edema and buphthalmos in a foal with congenital glaucoma. Intraocular pressures (IOP) were more than 80 mm Hg.



# SECTION I

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## Clinical Pharmacology

*Edited by Dr. Cynthia Kollias-Baker*

### CHAPTER 1.1

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## Neonatal Pharmacology and Therapeutics

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*Davis, California*

Several distinct features distinguish the disposition of drugs in neonatal foals and in adult horses. These differences are largely the result of age. Age brings with it susceptibility to disease and inherent physiologic differences that markedly alter the absorption, distribution, metabolism, elimination, and side effects of drugs. The predisposition of the neonate for septicemia and its sequelae, including sequestered infections such as arthritis and meningitis, also present challenges for pharmacologic intervention. This chapter reviews the physiologic differences of peripartum foals that influence the pharmacokinetics and pharmacodynamics of therapeutics in this age group. The chapter also highlights available drugs, particularly those in the antimicrobial category, for use in the treatment of neonates. Table 1.1-1 on the following page lists specific drug dosages.

Although the term *neonate* is used in this chapter to refer to foals less than 2 weeks of age, pharmacologic differences exist between a 1-day-old and a 7-day-old foal. Rapid physiologic and metabolic adaptations occur during the first few days of life; foals are relatively mature by 1 week of age. By the time they are 1 month of age, foals have metabolic and excretory capabilities similar to adult horses; however, because relative body fluid and fat reserves are still different at this age, drug disposition may be altered. Interindividual differences in pharmacokinetic disposition also exist among foals, preventing generalizations that overshadow the individual foal's particular level of maturity, unique physiology, and specific disease processes.

### PHYSIOLOGIC CONSIDERATIONS FOR DRUG THERAPY OF THE NEONATE

#### Dynamic Dosage Regimens

The rapidly changing body weight of neonatal foals necessitates frequent dosage adjustments, even within the same hospitalization period.

#### Altered Absorption

The extent of drug absorption in neonates is increased during the first week of life, compared with older foals and adult horses. This larger absorptive capacity results in an increased risk for toxicity from orally administered drugs. In addition, therapeutics that pass into the mare's milk can be absorbed across the neonatal gut. Nonpolar compounds in particular, such as chloramphenicol and erythromycin, are highly soluble in milk, and foals may absorb significant quantities while nursing. Another factor that affects gastrointestinal (GI) absorption in the postpartum period is the absence of an established luminal microbial population, which reduces bacterial metabolism of drugs. Altered gastric and duodenal pH concentration (high at birth), GI digestive capacity, biliary and exocrine pancreatic function, and motility associated with immaturity may also contribute to varying enteral absorption of drugs in neonates. Bioavailability after intramuscular (IM) administration may also differ in foals, with variations in tissue water and lipid content as well as local blood flow.

Table 1.1-1  
Selected Drug Doses for Neonatal Foals

Drug	Dosage	Instructions
<b>Antibiotics</b>		
amikacin	21-25 mg/kg IV q24h	Monitor renal function
amoxicillin	30 mg/kg PO q6-8h	Absorption possibly variable
ampicillin	20-25 mg/kg IV q8h	
penicillin, potassium	22,000-30,000 IU/kg IV q6h	
cefazolin	15-20 mg/kg IV q8h	First-generation cephalosporin
cefepime	11 mg/kg IV q8h	Fourth-generation cephalosporin
cefotaxime	20-50 mg/kg IV q6-8h	Third-generation cephalosporin
ceftazidime	20-50 mg/kg IV q6-12h	Third-generation cephalosporin
ceftiofur	4.4-10 mg/kg IV q12h	Third-generation cephalosporin
ceftizoxime	20-30 mg/kg IV q6-8h	Third-generation cephalosporin
ceftriaxone	20-50 mg/kg IV q12h	Third-generation cephalosporin
cephalexin	25 mg/kg PO q6h	First-generation cephalosporin
cephalothin	20 mg/kg IV q6h	First-generation cephalosporin
chloramphenicol	25-40 mg/kg PO q12h days 1-2 of life; q8h days 3-5; q6h >5 days	Potential human health hazard
doxycycline	10 mg/kg PO q12h	
gentamicin	6.6 mg/kg IV q24h	Monitor renal function
imipenem	15 mg/kg IV q6-8h	Slow infusion and diluted
rifampin	5 mg/kg PO q12h	Possible urine discoloration
ticarcillin-clavulanic acid	50 mg/kg IV q6h	Dose based on ticarcillin
metronidazole	10 mg/kg PO q8-12h	Monitor for neurotoxicity, hepatotoxicity
trimethoprim-sulfonamide	15-30 mg/kg PO q12h	
<b>Antifungal</b>		
fluconazole	Loading dose of 8.8 mg/kg followed by 4.4 mg/kg PO q24h	Monitor hepatic function
<b>NSAIDs</b>		
phenylbutazone	2 mg/kg IV PO q12-24h	Minimum dose and longest interval recommended; not to be used for more than 5 d; associated with GI ulcers, colitis, and renal crest necrosis
flunixin meglumine	0.25-0.5 mg/kg IV q12h 1 mg/kg IV q24h	As for phenylbutazone
ketoprofen	1-2.2 mg/kg IV q24h	As for phenylbutazone
<b>Treatment for Gastric Ulceration</b>		
famotidine	2.8-4 mg/kg PO q24h 0.5-2 mg/kg IV q24h	
ranitidine	6.6-8 mg/kg PO q8h 1.5 mg/kg IV q8-12h	
cimetidine	15-20 mg/kg PO q8h 6.6 mg/kg IV q6-8h	Possible association with seizures
omeprazole	1.5-4 mg/kg PO q24h	
misoprostol	2-5 µg/kg PO q8-12h	Monitor for diarrhea and colic
sucralfate	20-40 mg/kg PO q6h	Indication: mucosal ulcers
<b>Sedatives</b>		
diazepam	0.05-0.2 mg/kg IV, slow	
<b>Anticonvulsant Therapy</b>		
diazepam	0.1-0.4 mg/kg IV, slow	
phenobarbital	2-10 mg/kg IV q12-24h	Monitor for CNS, cardiac, and respiratory depression

PO, By mouth; q24h, every 24 hours; q12-24h, every 12 to 24 hours; IV, intravenous; GI, gastrointestinal; NSAIDs, nonsteroidal antiinflammatory drugs; CNS, central nervous system.

### Altered Volume of Distribution

Neonates have increased total body water (as much as 75% of body weight as compared with 60% to 70% in adults) and extracellular fluid volume (40% to 50% of body weight as compared with 22% in adults). This difference means that for an equivalent dose of polar or ionized drug (e.g.,  $\beta$ -lactam antibiotics, aminoglycosides, nonsteroidal antiinflammatory drugs [NSAIDs]), serum concentrations are lower in neonates because of a larger volume of distribution.

Lower body fat content reduces the volume of distribution of lipid-soluble (nonpolar) drugs and leads to relatively higher plasma concentrations. The clinical significance of this effect is minimal, however, because of the relatively low adipose tissue content of horses compared with other species. Albumin and plasma protein levels are also lower in neonates. The result is proportionately more unbound drug in plasma, thereby leading to greater availability of the active form. Although free drug concentrations may increase, the total plasma concentration of highly protein-bound drugs will be reduced. This phenomenon contributes to the increased volume of distribution of drugs carried by albumin, such as NSAIDs and erythromycin. The lower content of plasma globulins in foals may similarly affect the distribution of basic drugs. In addition, the blood-brain barrier permeability is relatively greater in foals, particularly during the first few days of life, thereby enhancing drug penetration into the central nervous system (CNS).

### Altered Metabolism

This feature primarily applies to lipid-soluble and nonpolar drugs, which undergo extensive hepatic metabolism to more polar compounds before excretion by the kidney or liver. Minor contributions to metabolism also exist from the GI mucosa, kidney, endothelium, skin, and lung. Examples of compounds that undergo extensive hepatic metabolism include chloramphenicol, methylxanthines, trimethoprim, sulfonamides, erythromycin, rifampin, metronidazole, and barbiturates. Although not studied specifically in foals, hepatic phase I (hydrolysis, oxidation, and reduction) and phase II (acetylation, glucuronide, and sulfate conjugation) reactions have decreased activity in neonates. Indirect evidence for this exists in foals because the elimination half-lives of many drugs decrease rapidly during the first week postpartum.

### Altered Elimination

The kidney, through glomerular filtration and tubular secretion, is the primary route of elimination for polar and ionized drugs, such as  $\beta$ -lactam and aminoglycoside antibiotics. The hepatic metabolites of nonpolar drugs are also eliminated through renal mechanisms. Biliary excretion is of secondary importance. Renal function is relatively mature in 2- to 4-day-old foals, as evidenced in studies of glomerular filtration rate and renal plasma flow. Thus renal elimination is not significantly different in neonates. A small degree of maturation does occur during the first several days of life, as evidenced by a more rapid clearance of aminoglycosides in foals from 1 to 10 days of

age. Because of a low urinary pH in foals, the reabsorption of weak bases may be reduced, whereas that of acids may be increased.

## THERAPEUTICS

Neonatal drug disposition, metabolism, and elimination should be considered in the creation of dosing plans for foals, particularly when dosages are extrapolated from adult values. Clinicians can adjust dosing protocols for many drugs for use in neonatal foals by increasing the dosage interval or reducing the magnitude of the dose. Drugs requiring extensive hepatic metabolism should be used judiciously in neonates, particularly in the first day or two of life. The effects of age on pharmacokinetic processes are compounded in premature foals and in those with disease states that alter GI integrity, plasma protein levels, fluid balance, and hepatic or renal function.

### Antimicrobials

The use of antimicrobials is central to clinical pharmacology of the equine neonate. Due to their inherent immunocompromised state on delivery, foals are at high risk for septic complications. Because the consequences of septicemia are so devastating, early and appropriate antibiotic therapy is critical. Antimicrobial administration should not be limited to foals with obvious signs of septicemia; rather, foals at risk for sepsis should be identified early and treated prophylactically.

Although blood cultures provide positive identification of sepsis as well as direction for antibiotic selection through quantitative susceptibility (minimum inhibitory concentration [MIC]) testing of isolates, they should not be relied upon solely. The sensitivity of blood cultures is variable and reported to be as low as 50% to 60% in some studies. In addition, culture results often take 1 day or more to complete, a delay that could certainly influence outcome. Suspicion of the presence of sepsis (e.g., sepsis score) should initiate antibiotic therapy. Drug selection should be made with a thorough knowledge of the likely etiologic agents involved and their predicted susceptibility patterns. The most common bacteria associated with septicemia in foals include enteric gram-negative microorganisms (particularly *Escherichia coli*) and nonenteric (*Actinobacillus/Pasteurella* bacteria) isolates. Gram-positive microbes such as streptococci, enterococci, and staphylococci can also participate as mixed or singular infections. Anaerobes have been documented to cause septicemia in foals. In light of these findings, broad-spectrum and bactericidal antibiotic regimens should be used, with an emphasis on enteric organisms. Clinicians are encouraged to record and become familiar with antibiotic susceptibility patterns of equine isolates in their specific practice area. Susceptibility results can vary widely among different geographic regions, even for similar bacterial isolates.

The combination of a  $\beta$ -lactam antibiotic such as penicillin or ampicillin and an aminoglycoside such as gentamicin or amikacin should provide adequate antimicrobial coverage in most cases of septicemia. First-generation cephalosporins such as cefazolin could substitute for penicillin or ampicillin. Alternatives such as

trimethoprim-sulfonamide combinations, chloramphenicol, and ticarcillin-clavulanate, are available but are less consistently effective against common pathogens in neonates. The use of such drugs should only follow susceptibility testing for the offending microbe. Ceftiofur has varying efficacy, with a greater proportion of isolates being susceptible when higher doses are used. This author initiates antimicrobial therapy with aminoglycoside and  $\beta$ -lactam antimicrobial combinations or ceftiofur until culture and susceptibility results are obtained. Aminoglycosides are potentially nephrotoxic, although amikacin may be slightly less so than gentamicin. In light of this fact, serum creatinine concentrations and urinalyses should be monitored in foals receiving these therapeutics. Clinical risk factors for the development of nephrotoxicity include prematurity, peripartum asphyxia, hypovolemia, hypotension, endotoxemia, and concurrently administered nephrotoxic drugs. Ototoxicity and vestibulotoxicity are other potential complications, although more difficult to test. Aminoglycosides are synergistic with penicillins and cephalosporins, as the latter allow for greater penetration of the bacterial cell envelope. Current recommendations for use of aminoglycosides in horses include a high dose with once-daily administration. This dosing protocol yields a higher peak plasma concentration of the drug that leads to more effective and rapid bactericidal potential as compared with previous multiple daily-dosing administrations. Similarly, the nephrotoxicity of such regimens should be reduced because they allow for more time when renal tubules are not exposed to threshold levels. Therapeutic drug monitoring is an ideal method used to monitor peak and trough plasma concentrations and allow for dosage adjustments.

Alternatives to the  $\beta$ -lactam/aminoglycoside combination include third-generation cephalosporins such as cefotaxime or ceftazidime, carbapenem  $\beta$ -lactams such as imipenem, and the newer fourth-generation cephalosporins. Clinicians should reserve use of these higher-generation cephalosporins or imipenem for foals with aminoglycoside-resistant, gram-negative microbes to avoid selection pressures favoring resistant bacteria. Other indications for their use include renal failure, which precludes the use of aminoglycosides, and meningitis, for which the cerebrospinal fluid (CSF) penetrability of the third-generation cephalosporins is advantageous. Ceftiofur does not share this feature. Recently, the pharmacokinetics of cefepime, a fourth-generation cephalosporin, has been evaluated in foals. The fourth-generation drugs have enhanced potency and extended spectra with both gram-positive and gram-negative coverage, including *Pseudomonas* spp. Imipenem is active against almost all clinically important aerobic and anaerobic gram-positive and gram-negative bacteria, with exceptions being enterococci and some isolates of *Staphylococcus* spp. and *Pseudomonas* spp.

The IM administration of antibiotics is often most practical in the field setting, which would apply to foals being prepared for referral to intensive care units, as well as those being treated prophylactically. The IM route is acceptable as long as foals are stable hemodynamically; use of the IM route requires adequate perfusion of the site for drug absorption. Ceftiofur, penicillin, and aminoglycosides are amenable to IM administration.

Duration of antibiotic therapy varies with the disease process. When used in a preventive manner in high-risk foals, a 3- to 5-day course is recommended. For foals with confirmed or suspected sepsis, antibiotic therapy should continue for at least 14 days. For localized infections such as abscesses or osteomyelitis, the length of treatment may need to be extended for as long as 1 to 2 months.

### Other Antimicrobials

Potentiated sulfonamides (e.g., trimethoprim-sulfonamides [TMS or SMZ]) are moderately broad-spectrum and can be administered orally. Despite this fact, these drugs cannot be recommended as first-line therapies for use in foals with documented or highly suspect sepsis because of resistance by many enteric isolates and streptococci. Sulfonamides readily penetrate the CSF, which makes them useful in the treatment of meningitis after a course of bactericidal therapy has been completed. Enrofloxacin, a fluoroquinolone, has excellent activity against gram-negative aerobes and staphylococci but should not be used in neonatal foals because of arthrotoxicity and subsequent cartilage erosions.

Tetracyclines are broad-spectrum antibiotics but are not considered optimal for sepsis because they are bacteriostatic and ineffective against many gram-negative microbes. High-dose oxytetracycline has been used to treat severe tendinous and ligamentous contracture in young foals, at a dose of 3 g per 50-kg foal (diluted in fluids and administered intravenously [IV]). Hydration status, serum creatinine concentration, and urinalyses should be monitored in such foals to minimize the risk of renal failure. Metronidazole has excellent activity against anaerobic bacteria and is particularly indicated in foals with clostridial enterocolitis, such as occurs with *Clostridium perfringens* or *Clostridium difficile*. Side effects including anorexia, neurologic signs, and hepatopathies from increased intestinal absorption in neonatal foals are not uncommon. To prevent these side effects this author uses a lower dose of 10 mg/kg, twice per day by mouth.

Chloramphenicol is another broad-spectrum oral drug; however, it is bacteriostatic. This drug is useful, as are TMS and doxycycline, when oral drugs are needed for longer-term therapy in the subacute to chronic stages of disease and when susceptibility patterns dictate their use. Rifampin is very effective against many staphylococci and penetrates tissues well. Amphotericin B and fluconazole can be used to treat fungemia and candidiasis in neonatal foals.

### Antiinflammatory Drugs

Use of NSAIDs in neonatal foals should be judicious. Clinicians should use caution in critically ill foals—such as those with hypoxic-ischemic insult and enteric or renal hypoperfusion—because such foals are at increased risk for adverse effects from NSAIDs. Septic foals often experience a systemic inflammatory response syndrome associated with endotoxemia or other inflammatory triggers. Although routine adult doses of NSAIDs can have adverse effects in compromised neonates, such as reductions in GI mucosal and renal perfusion, low doses may help mitigate prostaglandin and thromboxane production. Flunixin meglumine and ketoprofen appear to be less nephrotoxic

and insulting to the GI tract than phenylbutazone. Low doses of flunixin meglumine may provide some anti-inflammatory effect with a reduced risk of complications.

Provisions for analgesia, such as for orthopedic problems, may require higher doses of NSAIDs. Given the longer elimination half-lives in neonates as compared with adult horses, as well as the relative hypoproteinemia of foals, clinicians should use the lowest possible dose to achieve the desired effects. Dosing intervals should also be maximized. Chronic administration of these drugs should be avoided to prevent development of GI ulceration and renal papillary necrosis. Because the potential for toxicity is greatest with phenylbutazone, this author prefers to use flunixin meglumine or ketoprofen for these purposes. Concurrent administration of antiulcer medication or misoprostol may be indicated. The pharmacokinetics of ibuprofen has recently been studied in foals, making this drug a potential therapeutic agent. Carprofen has been used in adult horses but requires further study in foals.

### Therapy for Gastric Ulcers

The routine prophylactic use of antiulcer medications in critically ill foals has been questioned. Prolonged reduction of gastric acid production can increase gastric bacterial colonization in human neonates. In addition, many critically ill foals have a continuously alkaline pH. When gastric ulcer disease is present, therapy should include a combination of antiulcer medication and maintenance of GI oxygen delivery. Gastric ulceration can be treated with H<sub>2</sub>-histamine receptor antagonists or proton-pump inhibitors such as omeprazole. This author prefers ranitidine to cimetidine because of potency and because cimetidine has been associated with seizurelike activity and a reduction in hepatic microsomal enzyme metabolism. Omeprazole is a potent inhibitor of gastric acid secretion in horses and foals. Misoprostol, a synthetic analogue of prostaglandin E<sub>1</sub>, can be administered if ulceration is associated with the use of NSAIDs. The use of omeprazole and misoprostol in neonates requires further study. Sucralfate may bind mucosal ulcers, increase local mucus and bicarbonate secretion, and enhance mucosal blood flow. In addition to the use of pharmaceuticals, fluid balance and blood pressure should be monitored; reduced oxygen delivery as occurs with ischemia or hypoperfusion may contribute to GI failure and ulcers.

### Sedatives

Sedation for neonatal foals is best achieved with diazepam. Diazepam provides excellent sedation and muscle

relaxation with minimal cardiovascular effects. Acepromazine should not be used in neonates because of its hypotensive effects. The  $\alpha_2$ -agonists such as xylazine and detomidine should be used with caution in sick neonatal foals because of the risk of significant bradycardia, hypotension, and respiratory depression.

### Seizure Control

Diazepam is also quite useful in controlling seizures. Phenobarbital can be used for recurrent or persistent seizure disorders. Serum levels of phenobarbital should be monitored; the therapeutic goal extrapolated from other species is 15 to 40  $\mu\text{g/ml}$ . The administration of higher doses can cause ataxia, respiratory depression, and hypotension. Acepromazine should not be used in foals with seizures because it lowers the seizure threshold.

### Therapy for Meconium Impaction

Refractory meconium impactions can be treated with retention enemas that contain acetylcysteine. A solution of 4% acetylcysteine in water is made and administered through a 30 French Foley catheter with a 30-cc balloon tip. The clinician should gently insert the catheter into the foal's rectum and slowly inflate the balloon while the enema solution (4 to 6 oz) is allowed to passively flow into the rectum. The foal is kept sedated for 20 to 45 minutes while the enema and catheter are kept in place.

### Supplemental Readings

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## CHAPTER 1.2

# Antimicrobial Therapy for Horses

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Antibiotic therapy for horses presents unique challenges because horses do not absorb some oral medications and the cost of many drugs makes their use impractical. Clinicians often use drugs formulated for humans in horses but encounter problems with reformulating the dose for convenient administration. In addition, horses are prone to adverse reactions that limit the use of some drugs. Oral lincosamides, for example, may disrupt the intestinal bacteria and cause enteritis in horses, and fluoroquinolones should not be administered to young horses because of the risk of injury to the developing articular cartilage. Drug treatment for foals carries additional challenges because of differences in drug disposition in foals versus adults and because foals are often immunocompromised at the time of treatment. Although these factors present challenges, it is essential that horses receive appropriate and rational therapy. Failure to provide appropriate antibiotic therapy may result in drug resistance and ineffective treatment.

### BACTERIA ENCOUNTERED IN HORSES

The most commonly encountered gram-negative bacteria in horses include *Escherichia coli*, *Pasteurella* spp., *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Enterobacter* spp. Gram-positive bacteria include the  $\beta$ -hemolytic streptococci and *Staphylococcus aureus*. Other atypical bacteria of importance are *Rhodococcus equi* and *Actinobacillus equuli*. The most common anaerobic bacteria encountered are *Bacteroides* spp. and *Clostridium* spp.

Antibiotic selection is simplified if bacteria are accurately identified because the susceptibility patterns for many organisms are predictable. For example, if the bacteria are *Pasteurella* spp. or *Streptococcus* spp., susceptibility to penicillin or an aminopenicillin such as ampicillin or a trimethoprim-sulfonamide is expected. The relative susceptibilities of some common isolates to antibiotics frequently used in horses are listed in Table 1.2-1.

In horses, anaerobic bacteria that cause infection include *Clostridium* spp., *Fusobacterium* spp., *Peptostreptococcus* spp., and *Bacteroides* spp. These bacteria usually are sensitive to a penicillin, chloramphenicol, or metronidazole. Other drugs often used to treat anaerobic infections in small animals and humans are clindamycin, amoxicillin-clavulanate, or one of the second-generation cephalosporins, such as cefotetan or cefoxitin. These drugs are not used in horses, however, because of poor absorption (amoxicillin-clavulanate), toxicity (clindamycin) or high expense (cephalosporins). Resistance

in the *Bacteroides fragilis* group is a more common problem because these organisms can produce a  $\beta$ -lactamase that inactivates first-generation cephalosporins, penicillins, ampicillin, and amoxicillin. Metronidazole can be selected for refractory and serious infections caused by anaerobes because it is consistently active against these organisms, including *B. fragilis*. The activity of cephalosporins or trimethoprim-sulfonamides for anaerobic infections is unpredictable. None of the aminoglycosides (gentamicin, amikacin) and only the newest generation of fluoroquinolones (e.g., moxifloxacin, gatifloxacin) are active against anaerobic bacteria. The use of these new-generation fluoroquinolones has not been reported in horses, and their safe use has not been determined. The older fluoroquinolones such as enrofloxacin and orbifloxacin have poor activity against anaerobic bacteria.

### Problem Bacteria

Because antibiotic resistance can commonly occur in *P. aeruginosa*, *Enterobacter* spp., *Klebsiella* spp., *E. coli*, and *Proteus* organisms (especially indole-positive *Proteus* spp.), susceptibility testing is advised for these isolates. Many *E. coli* isolates can be resistant to the commonly used antibiotics such as penicillins, aminopenicillins, first-generation cephalosporins, and tetracyclines, and although susceptibility to chloramphenicol and trimethoprim-sulfonamides is possible, it is unpredictable.

On the basis of published susceptibility data, gram-negative enteric bacteria can be expected to be susceptible to fluoroquinolones and aminoglycosides. Resistance to fluoroquinolones has been observed in small animals, however, and may be increasing. Resistance to gentamicin among equine pathogens has also been documented in veterinary teaching hospitals, and therefore amikacin is the most active of the aminoglycosides against gram-negative bacteria in horses, including *P. aeruginosa*. Extended-spectrum cephalosporins (second- or third-generation cephalosporins) are usually active against enteric gram negative bacteria, but may not be active against *P. aeruginosa*. Although *P. aeruginosa* is inherently resistant to many drugs, it may be susceptible to fluoroquinolones, aminoglycosides, or an extended-spectrum penicillin, such as ticarcillin or piperacillin.

The extended-spectrum cephalosporins (second-, third-, and fourth-generation cephalosporins) have been used for some of the refractory gram-negative infections, but only ceftazidime is active against *P. aeruginosa*. The expense of most of these human drugs, however, is almost prohibi-

**Table 1.2-1**  
**Drug Selection for Equine Bacterial Pathogens**

Pathogen	Drug Choice	Second Choice
<b>Gram-Positive</b>		
<i>Rhodococcus equi</i>	erythromycin +/- rifampin	azithromycin
<i>Streptococcus</i> spp.	penicillin G, ampicillin, ceftiofur	trimethoprim-sulfonamides, erythromycin, chloramphenicol
<i>Staphylococcus aureus</i>	trimethoprim-sulfonamide	enrofloxacin, chloramphenicol, gentamicin
<b>Gram-Negative</b>		
<i>Escherichia coli</i>	gentamicin, amikacin	ceftiofur, enrofloxacin, orbifloxacin, trimethoprim-sulfonamide
<i>Klebsiella pneumoniae</i>	gentamicin, amikacin	ceftiofur, enrofloxacin, orbifloxacin, trimethoprim-sulfonamide
<i>Enterobacter</i> spp.	gentamicin, amikacin	ceftiofur, enrofloxacin, trimethoprim-sulfonamide
<i>Pseudomonas aeruginosa</i>	gentamicin, amikacin, ticarcillin	enrofloxacin, cefepime, ceftazidime
<i>Pasteurella</i> spp.	ampicillin, ceftiofur, trimethoprim-sulfonamide	enrofloxacin, orbifloxacin, chloramphenicol, tetracycline
<i>Actinobacillus</i> spp.	ampicillin, penicillin, trimethoprim-sulfonamides	enrofloxacin, orbifloxacin, chloramphenicol

tive for routine use in horses, and therefore drugs such as cefotaxime, ceftazidime, and cefepime have been used only to a small extent. Dosages for these drugs are listed in Table 1.2-2.

## DRUG ABSORPTION

### Parenteral Administration

Many antibiotics can be administered via the intravenous (IV) route, a mode that rapidly delivers high concentrations to tissues. Intramuscular (IM) administration also is suitable for many drugs, although pain and muscle injury from injection can be serious drawbacks. The absorption from an IM injection is usually complete, and high plasma concentrations are attained rapidly. For some drugs, however, slow release of the drug from the IM injection site may effectively prolong the dosing interval. The site of an IM injection also affects drug absorption. Studies in horses and cattle have shown that for many drugs, an injection in the neck muscle is absorbed more rapidly and completely than an injection in the gluteal or hamstring muscle (semitendinosus).

### Oral Administration

Absorption after oral administration is low in horses for many drugs. Aminopenicillins (ampicillin, amoxicillin), cephalosporins, and macrolide antibiotics are not absorbed as rapidly or to as great an extent as they are in small animals and humans. This low absorption limits the use of the oral route of administration to only a few drugs for horses. Oral administration of antibiotics to foals, however, may be practical and effective because they appear to exhibit greater absorption from the gastrointestinal (GI) tract than do adult horses. For example, systemic availability of amoxicillin in adult horses is only 2% to

10% after oral administration, but absorption of the same drug in foals is somewhat better—36% to 42% after oral administration. Cefadroxil also has relatively good absorption in foals (but not in adult horses) after oral administration, with a mean systemic availability of 58%.

Modification of some drugs has improved oral absorption in horses. For example, when erythromycin base is administered orally to horses, it is rapidly degraded into inactive metabolites in the equine stomach and intestine, resulting in poor systemic availability of the drug. However, if erythromycin is administered orally as an ester pro-drug, such as erythromycin estolate, it is absorbed as the intact ester and converted to the active drug after absorption. Oral absorption is also improved if erythromycin is administered as a phosphate salt whereby it resists degradation in the stomach and intestine and is absorbed as active erythromycin.

The interactions caused by oral administration of drugs with food or interfering drugs also can reduce absorption. The presence of ingesta decreases the oral absorption of microencapsulated erythromycin in horses compared with fasted animals. In addition, oral administration of drugs that contain cations ( $\text{Fe}^{+3}$ ,  $\text{Al}^{+3}$ ) significantly inhibit oral absorption of fluoroquinolones. Compounds that may contain these cations include antacids, sucralfate, and iron supplements.

### Local Drug Administration

Direct drug administration has been used to provide high concentrations of drugs in bones and joints of horses and decrease reliance on high systemic doses. Intraarticular administration of gentamicin to horses produces high synovial drug concentrations. Drug clearance from joint fluid is slower than from the plasma, and therefore intraarticular administration may provide effective concentrations for at least 24 hours. High concentrations in the



**Table 1.2-2**  
**Appropriate Doses for Antibiotics\***

Drug	Brand Name	Dosing Information
amikacin	Amiglyde-V	Adults: 10 mg/kg IM, IV q24h Foals: 20-25 mg/kg IM, IV q24h
ampicillin	Amp-Equine (and generic)	6.6 mg/kg to 10-20 mg/kg IM, IV q6-8h (Doses as high as 25 to 40 mg/kg q6-8h have been used for refractory infections.)
amoxicillin azithromycin	Amoxi-inject Zithromax	10-20 mg/kg IM; not absorbed well orally, except in foals For <i>Rhodococcus equi</i> , 10 mg/kg orally q24h for first week, then q48h thereafter (suggested dose only; has not been tested for efficacy)
cefadroxil	Cefa-Tabs	30 mg/kg oral q12h (not in adults; oral absorption adequate only in young foals)
cefazolin cefepime	Ancef, Kefzol Maxipime	25 mg/kg IV, IM q6-8h Adults, 6 mg/kg IV q8h Foals: 11 mg/kg IV q8h
cefoxitin	Mefoxin	20 mg/kg IV IM q4-6 hr
cefotaxime	Claforan	Foals: 40 mg/kg q6h IV
ceftiofur	Naxcel	2.2 mg/kg q12h IM to as much as 11 mg/kg/day IM
cephapirin	Cefadyl, generic	20-30 mg/kg q4-8h, IM, IV
chloramphenicol	Chloromycetin and generic	35-50 mg/kg PO q6-8h
doxycycline	Vibramycin and generic	10 mg/kg q12h PO (Do not administer IV.)
enrofloxacin	Baytril and Baytril-100	5 mg/kg q24h IV, IM; 7.5-10 mg/kg q24h PO (not for use in foals)
erythromycin	Generic	(NOTE: Plain tablets are poorly absorbed in horses. Use erythromycin estolate.) Erythromycin estolate: for treatment of <i>Rhodococcus</i> infection, 25 mg/kg q6h PO Erythromycin phosphate or Erythromycin estolate: 37.5 mg/kg q12h or 25 mg/kg q8h PO Erythromycin gluceptate injection: foals 5 mg/kg q 4-6h IV Do not administer to horses until more safety data becomes available.
florfenicol	Nuflor	
gentamicin	Gentocin	Adult: 4 mg/kg IV, IM q24h to 6.8 mg/kg IV, IM q24h Foal (<2 weeks): 12-14 mg/kg q24h, IM, IV
metronidazole	Flagyl (and generic)	10 mg/kg q12h oral
orbifloxacin	Orbax	2.5-5 mg/kg q24h PO
oxytetracycline	LA-200 (and other forms)	Ehrlichiosis: 3.5 mg/kg q12h and as much as 10 mg/kg q24h IV, IM (IV slowly) Foals (flexural limb deformities): As much as 44 and up to 70 mg/kg IV (2-3 g per foal) with two doses given 24 hours apart have been used
penicillin G	Generic	Penicillin potassium: 20,000 U/kg q6-8 hr IV Penicillin sodium: 20,000 U/kg q6-8 hr IV Penicillin procaine: 20,000 to 24,000 U/kg q12-24h IM
pyrimethamine rifampin	Daraprim Rifadin	1 mg/kg q24h PO (in combination with a sulfonamide) 10 mg/kg q24h PO Foals with <i>Rhodococcus</i> infection: 5 mg/kg q12h PO (with erythromycin)
sulfonamides	Generic	See trimethoprim-sulfonamides
ticarcillin	Ticar	44 mg/kg q6-8h, IV, IM; also used intrauterine in mares
tilmicosin	Micotil	Do not use in horses until more safety data becomes available.
trimethoprim-sulfadiazine or trimethoprim-sulfamethoxazole	Tribissen, Uniprim, Bactrim	25 mg/kg sulfonamide + 5 mg/kg trimethoprim (30 mg/kg total) PO q12-24h

PO, By mouth; IM, intramuscular; IV, intravenous; q24h, every 24 hours; q6-8h, every 6 to 8 hours.

\*Many of the doses listed are extra-label or are human drugs used in an off-label or extra-label manner. Doses listed are based on best available evidence at the time of table preparation; however, the author cannot ensure the efficacy of drugs used according to recommendations in this table. Adverse effects may be possible from drugs listed in this table of which the author was not aware at the time of table preparation. Veterinarians using these tables are encouraged to check current literature, product labels, and manufacturer's disclosures for information regarding efficacy and any known adverse effects or contraindications not identified at the time of preparation of this table.

limbs also can be achieved through regional limb perfusion. In this technique, an infected limb is perfused with an antibiotic and a temporary tourniquet applied to the limb proximal to the site of drug administration to maintain a high drug concentration.

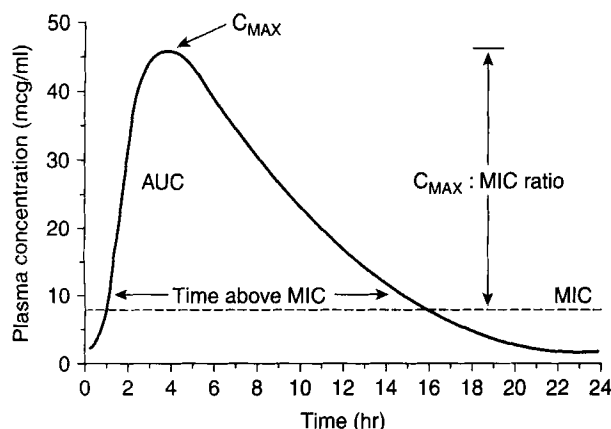
## PHARMACOKINETIC-PHARMACODYNAMIC OPTIMIZATION OF DOSES

To achieve a cure the drug concentration in plasma, serum, or tissue fluid should be maintained above the minimum inhibitory concentration (MIC) or some multiple of the MIC for at least a portion of the dose interval. Antibacterial dosage regimens are based on this assumption, but drugs vary with respect to the magnitude of the peak concentration and the time above the MIC that is required for a clinical cure. Pharmacokinetic-pharmacodynamic (PK-PD) relationships for antibiotics attempt to describe the way these factors can correlate with clinical outcomes. Figure 1.2-1 illustrates terms used to describe the shape of the plasma concentration versus the time profile. The  $C_{MAX}$  is simply the maximum plasma concentration attained during a dosing interval. The  $C_{MAX}$  is related to the MIC by the  $C_{MAX}:MIC$  ratio. The AUC is the total area under the curve. The AUC for a 24-hour period is related to the MIC value by the  $AUC:MIC$  ratio. Also shown in Figure 1.2-1 is the time in hours during which plasma concentration exceeds MIC ( $T > MIC$ ).

Antibiotics can be *bactericidal* or *bacteriostatic* depending on the drug and the organism. A bactericidal drug may be either concentration-dependent or time-dependent. If the activity is concentration-dependent, the dose administered should be high enough to maximize the  $C_{MAX}:MIC$  or  $AUC:MIC$  ratio. If the activity is time-dependent, the drug should be administered frequently enough to maximize the time when plasma concentration exceeds the MIC.

### Aminoglycosides

Aminoglycosides (e.g., gentamicin and amikacin) are concentration-dependent bactericidal drugs; therefore the



**Figure 1.2-1** Plasma concentration versus time profile and MIC. Relationship between MIC and pharmacokinetic terms are shown.  $C_{MAX}$ , Maximum plasma concentration attained during a dosing interval;  $MIC$ , minimum inhibitory concentration;  $AUC$ , total area under the curve.

higher the drug concentration, the greater the bactericidal effect. An optimal bactericidal effect occurs if a high enough dose is administered to produce a peak serum concentration that is 8 to 10 times the MIC of the organism. This effect can be achieved with administration of a single dose once daily. This regimen is at least as effective, and perhaps less nephrotoxic, than the administration of lower doses more frequently. A regimen that uses this dosing strategy in an animal is reflected in the doses listed in Table 1.2-2.

### Fluoroquinolones

No published studies involving horses exist that indicate which pharmacokinetic parameters are predictive of a clinical cure in horses. In other species, however, a  $C_{MAX}:MIC$  of 8 to 10 or an  $AUC:MIC$  of 30 to 125 has been associated with a cure. As with the aminoglycosides, the current dose recommendations listed in Table 1.2-2 reflect this understanding and take into consideration that most equine gram-negative pathogens (especially *Enterobacteriaceae*) have MIC values of 0.125  $\mu\text{g/ml}$  or less.

### $\beta$ -Lactam Antibiotics

$\beta$ -lactam antibiotics such as penicillins, potentiated-aminopenicillins, and cephalosporins are slowly bactericidal. Their concentrations should be kept above the MIC throughout most of the dosing interval (long  $T > MIC$ ) for the optimal bactericidal effect. Dosage regimens for the  $\beta$ -lactam antibiotics should consider these pharmacodynamic relationships. To treat a gram-negative infection, especially a serious one, some regimens for penicillins and cephalosporins require administration 3 to 4 times per day. Gram-positive organisms are more susceptible to  $\beta$ -lactam antibiotics and produce a greater bactericidal effect in these organisms compared with gram-negative bacteria. Additionally, because the MICs are lower for gram-positive bacteria and because antibacterial effects (postantibiotic effect [PAE]) occur at concentrations below the MIC, longer dose intervals may be possible for infections caused by gram-positive compared with gram-negative bacteria.

### Bacteriostatic Drugs

Drugs such as tetracyclines, macrolides (erythromycin and derivatives), sulfonamides, lincosamides (lincomycin and clindamycin), and chloramphenicol derivatives act in a bacteriostatic manner against most bacteria. Against susceptible gram-positive bacteria, however, the macrolides appear to be bactericidal and can demonstrate a postantibiotic effect. Chloramphenicol also can produce a bactericidal effect if the organism is very susceptible. Bacteriostatic drugs are the most effective when the drug concentrations are maintained above the MIC throughout the dose interval. In this way, they act in a time-dependent manner.

## UPDATE ON ANTIBACTERIAL DRUGS

### Fluoroquinolone Antimicrobials

Fluoroquinolone antimicrobial drugs have been available for humans and small animals for more than 10 years. The first drug in this group for veterinary use was enrofloxacin.

Multiple studies and clinical experiences have shown that this class of drugs can be valuable in the treatment of infections in horses. The drugs' valuable properties include the following:

1. The ability to be administered by various routes, such as oral, IV, or IM (although only enrofloxacin is available in an injectable formulation in the United States)
2. A spectrum of activity that includes staphylococci and gram-negative bacilli such as *K. pneumoniae*, *E. coli*, and *Proteus* spp.
3. A spectrum of activity that does not include anaerobic bacteria and therefore poses little risk to the disruption of bacteria in the GI tract
4. A good safety profile in adult horses

The spectrum of activity includes bacteria that may otherwise require injectable drugs, or drugs that could carry a risk of adverse effects. It is important to recognize that the spectrum does not include *Streptococcus* spp. or anaerobic bacteria and that the concentrations needed for activity against *P. aeruginosa* may require doses that have not been tested for safety in horses.

As noted in Table 1.2-2, an injectable dose of enrofloxacin of 2.5 to 5 mg/kg once daily or an oral dose of 7.5 to 10 mg/kg once daily is recommended. For orbifloxacin, an oral dose of 2.5 to 5 mg/kg once daily is recommended. Ciprofloxacin (Cipro, registered for human use) is not recommended for use in horses because absorption after oral administration is poor. The methods of administration for horses have been (1) to crush up tablets used in small animals, (2) to administer the injectable solution (either 2.27% or 10%) either IM (neck muscle) or IV, or (3) to administer the concentrated 10% solution orally. All three methods appear to be safe and to produce adequate plasma concentrations, except for the administration of the concentrated 10% solution orally. This solution produces inconsistent and incomplete absorption in horses, possibly because of its insolubility in solutions of low pH.

The safety profile of fluoroquinolones in horses is good; the most significant adverse effect has been noted in foals. In studies performed in healthy foals a dose of 10 mg/kg/day orally for 1 week produced severe lesions of the articular cartilage in foals. Some foals began to show clinical signs of joint injury after only 4 days of treatment. Studies performed in adult horses have shown that enrofloxacin administration does not cause lesions of the articular cartilage of adults. Problems with tendinitis reported in humans, including tendon rupture, have not been observed in horses.

### Azithromycin

New macrolide antibiotics represent another class of drugs currently under consideration for use in horses. The prototypical macrolide antibiotic is erythromycin. Because of poor absorption and adverse effects (diarrhea) new drugs have been developed that have better pharmacokinetic properties and an improved spectrum of activity and are better-tolerated. The new macrolides include clarithromycin and tilmicosin. Macrolide derivatives include the azalide azithromycin (Zithromax). The use of clar-

ithromycin has not been reported in horses. Tilmicosin is being tested for use in horses, but its pharmacokinetic properties and safety have not yet been reported.

Azithromycin has a half-life of 11 and 16 hours in foals after oral and IV dosing, respectively. The absorption of azithromycin in foals after oral administration is 33%, which is similar to the systemic availability found in humans, and the volume of distribution is very high at 12 L/kg. One of the distinct advantages of azithromycin is its ability to concentrate in leukocytes for extended periods of time. The concentration of azithromycin in polymorphonuclear cells reached a level that was 200 times the plasma concentration, had a half-life of more than 50 hours, and was above a concentration of 5.68 µg/ml (the MIC breakpoint for susceptible organisms being less than or equal to 2.0 µg/ml) for 120 hours after administration.

Clinical experience with azithromycin has indicated that it is safe for use in foals for the treatment of *R. equi* infections, but no published reports exist of controlled efficacy studies. On the basis of pharmacokinetic data and clinical experience, veterinarians have used azithromycin in foals at a dose of 10 mg/kg once daily initially, followed by 10 mg/kg every other day orally after clinical improvement is observed.

### Cephalosporins

Cephalosporin antibiotics have many advantages, including broad-spectrum activity and a good safety profile. Several cephalosporins have been studied in horses for clinical use, including the first-generation cephalosporins cefazolin, cephapirin, and cefadroxil; the second-generation cephalosporin cefoxitin; and the third-generation cephalosporins ceftiofur and ceftriaxone.

The only drug approved for use in a veterinary species that meets the criteria for an extended-spectrum cephalosporin is ceftiofur, 50 mg/ml (Naxcel), which is registered for horses. Ceftiofur is metabolized quickly to an active metabolite, desfuroylceftiofur, as well as other metabolites. Desfuroylceftiofur has activity that resembles a third-generation cephalosporin *in vitro*. Ceftiofur is approved for use in horses for treatment of respiratory tract infections at a dose of 2.2 to 4.4 mg/kg every 24 hours IM. However, higher doses have been recommended for the treatment of gram-negative organisms (e.g., *Klebsiella* spp., *Enterobacter* spp., and salmonellae). For example, many of the gram-negative bacteria from horses have ceftiofur MIC values near 1.0 µg/ml, and the maintenance of concentrations at or above this level in foals would require a calculated dose of 4.4 mg/kg every 8 hours and in adults 5.5 mg/kg every 8 to 12 hours, which is above the label dose. Clinicians should maintain the concentrations above the MIC for as long as possible when using ceftiofur because the drug is not expected to have a PAE against gram-negative bacteria. Other studies in foals have indicated that a dose of 2.2 to 6.6 mg/kg could be given to foals every 12 hours IM for treatment of neonatal sepsis. Toxicity studies have shown that horses tolerate doses as high as 11 mg/kg per day IM; pain at the injection site and decreased feed consumption are the most commonly observed side effects at the highest dose.

The newest developments in the cephalosporin class

are the fourth-generation drugs represented by cefepime. Cefepime (Maxipime) has an increased spectrum of activity compared with other cephalosporins and is broad enough to include both gram-positive and gram-negative bacteria. Cefepime is active against *P. aeruginosa* as well as *K. pneumoniae* and *E. coli*, which are resistant to other drugs. Cefepime pharmacokinetics have been studied in foals and mares. Although clearance was rapid, this drug potentially could be used for resistant infections. A dose of 11 and 6 mg/kg IV every 8 hours was derived for foals and for adults, respectively. When cefepime was administered to horses orally, signs of colic were observed.

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## CHAPTER 1.3

# Nonsteroidal Antiinflammatory Drugs

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The most commonly used drugs for control of pain and inflammation in horses are the nonsteroidal antiinflammatory drugs (NSAIDs). NSAIDs inhibit the enzyme cyclooxygenase (COX), which converts arachidonic acid to prostaglandins, thromboxanes, and prostacyclin. Blocking these eicosanoids results in analgesic, antipyretic, antithrombotic, antientotoxic, and antiinflammatory effects. Two distinct forms of COX have been demonstrated recently. The constitutively expressed form (normal for homeostasis) is referred to as *COX-1*, and the inducible form (that occurs in response to injury) is referred to as *COX-2*. COX-1 is found in platelets, the kidneys, and the gastrointestinal (GI) tract, and COX-2 has been identified in fibroblasts, chondrocytes, macrophages, mesangial cells, and endothelial cells. COX-2 is induced by exposure to various cytokines, mitogens, and endotoxin and is up-regulated at inflammation sites.

Unfortunately, this classification is now determined to be too simplistic to explain the roles of the different forms of cyclooxygenase. It now appears that COX-2 can be produced constitutively in the brain, bone, lung, kidney, thymus, prostate, spinal cord, ovary, uterus, placenta, cartilage, synovia, and endothelia and can be induced by hormones, cytokines, nitric oxide, and lipxygenase products. COX-2 is involved in cellular processes, including

gene expression, differentiation, mitogenesis, apoptosis, bone modeling, wound healing, and neoplasia.

The prostaglandins produced in the GI tract and the kidney that maintain mucosal integrity in the upper GI tract and renal perfusion appear to be derived from COX-1. Suppression of COX-1 activity with NSAIDs therefore is believed to be critical to the development of toxicity. Researchers have suggested that COX-2-selective NSAIDs would suppress prostaglandin synthesis at sites of inflammation but would spare constitutive prostaglandin synthesis in the GI tract and kidney. Currently available NSAIDs vary in their potency as inhibitors of COX-1, but virtually all are far more potent inhibitors of COX-2.

Pharmaceutical companies have raced to develop COX-2-selective NSAIDs, but these drugs do not appear to be the perfect solution. If COX-2 is primarily responsible for the prostaglandins that mediate pain, inflammation, and fever, then COX-2-selective drugs should be more effective. However, the available NSAIDs already effectively inhibit COX-2. In addition, it has now been shown that COX-1-derived prostaglandins contribute to pain, inflammation, and fever, so COX-2-selective NSAIDs may be less effective. Studies now published show that some COX-2-selective drugs are only therapeutically effective at doses high enough to inhibit COX-1. Also, COX-2 may

are the fourth-generation drugs represented by cefepime. Cefepime (Maxipime) has an increased spectrum of activity compared with other cephalosporins and is broad enough to include both gram-positive and gram-negative bacteria. Cefepime is active against *P. aeruginosa* as well as *K. pneumoniae* and *E. coli*, which are resistant to other drugs. Cefepime pharmacokinetics have been studied in foals and mares. Although clearance was rapid, this drug potentially could be used for resistant infections. A dose of 11 and 6 mg/kg IV every 8 hours was derived for foals and for adults, respectively. When cefepime was administered to horses orally, signs of colic were observed.

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produce beneficial prostaglandins; highly selective COX-2 inhibitors may therefore produce adverse reactions not seen with existing NSAIDs. Finally, because most GI ulceration is associated with significant mucosal inflammation, it is likely that COX-2 is expressed in these circumstances and that the derived prostaglandins are responsible for promoting healing. NSAIDs are well-known to retard the healing of ulcers and exacerbate inflammatory bowel disease.

NSAIDs are primarily antiinflammatory because of their inhibition of prostaglandin production. NSAIDs therefore do not resolve inflammation but prevent its ongoing occurrence. So although prostaglandin production rapidly diminishes with the use of NSAIDs, any previously present prostaglandin must be removed before inflammation subsides. Peak concentrations of phenylbutazone, ketoprofen, and carprofen are delayed at the site of inflammation and persist for longer periods in inflammatory exudates than in plasma. This phenomenon explains the delayed onset and prolonged duration of antiinflammatory action that does not correlate with plasma pharmacokinetics.

COX inhibition does not explain all the antiinflammatory activity of NSAIDs. NSAIDs are more lipophilic at the low pH found in inflamed tissues. Some antiinflammatory action appears to be related to NSAIDs' ability to insert into the lipid bilayer of cells and disrupt normal signals and protein-protein interactions in cell membranes. In the cell membranes of neutrophils, NSAIDs inhibit neutrophil aggregation, decrease enzyme release and superoxide generation, and inhibit lipooxygenase.

NSAIDs act as analgesics by inhibiting COX and preventing the production of prostaglandins that sensitize the afferent nociceptors at peripheral sites of inflammation. Increasing evidence exists, however, that some NSAIDs have a central mechanism of action for analgesia and act synergistically with opioids. Therefore in the management of pain and inflammation in horses NSAIDs are more effective as analgesics when inflammation is a part of the pain process and when they are given before the onset of the inflammatory process or insult. The time to onset and duration of analgesia of NSAIDs does not correlate well with their antiinflammatory properties. The analgesic effect has a more rapid onset and shorter duration of action than the antiinflammatory effect, so dosage regimens for effective analgesia necessarily may differ from those for antiinflammatory effects.

### ADVERSE EFFECTS OF NONSTEROIDAL ANTIINFLAMMATORY DRUGS

The adverse effects of the NSAIDs are related to COX inhibition in tissues where prostaglandins are beneficial and protective. Bleeding tendencies, for example, might develop because platelet aggregation is classically inhibited by NSAIDs, which prevent thromboxane production through the COX-1 pathway. Recovery of platelet function depends on the pharmacokinetics of the NSAID and the mechanism of COX inhibition. For example, aspirin permanently modifies COX, so platelet function is only restored by the production of new platelets. In the GI tract, prostaglandins are natural inhibitors of gastric acid secretion and support mucosal blood flow. NSAID inhibi-

tion of prostaglandin biosynthesis results in increased acidity and decreased mucosal blood flow and mucous production, leading to ulcer formation. In general, the NSAIDs have a higher incidence of toxicity in neonates because kidney and liver function is not fully developed. When indicated in neonates, NSAIDs should be administered at the lowest possible doses and at extended dosing intervals. NSAIDs also should be administered very cautiously to dehydrated animals. Because NSAIDs predominantly distribute in extracellular water, plasma concentrations are greater than normal in the dehydrated animal and more likely to cause toxicity. The NSAIDs should not be used in conjunction with glucocorticoids because the latter potentiate the former's GI toxicity.

The renal toxicity of NSAIDs is a major concern, particularly in the perioperative period. NSAIDs typically have little effect on renal function in normal animals. However, they decrease renal blood flow and glomerular filtration rate, however, in animals with congestive heart failure, those that are hypotensive or hypovolemic (especially during anesthesia and surgery), or those that have chronic renal disease. Under these circumstances, acute renal failure may be precipitated as NSAIDs block the ability of renal prostaglandins to mitigate the vasoconstrictive effects of norepinephrine and angiotensin II on glomerular arteries. COX-1 is currently thought to be responsible for renal prostaglandin production; COX-2-selective drugs may prevent this problem. A more severe dose-dependent toxicity associated most commonly with phenylbutazone is renal papillary necrosis. Although attributed to impaired renal blood flow, other mechanisms, such as direct nephrotoxicity of the drug or its metabolites, also may be involved.

### SPECIFIC AGENTS

#### Aspirin

Aspirin is only available in oral forms. Because it is a weak acid, it is best absorbed in the acidic environment of the upper GI tract. During absorption, aspirin is partially hydrolyzed to salicylic acid and distributed throughout the body. The extent of protein binding is moderate, approximately 60%, and depends on the species and the drug and albumin concentrations. Aspirin is metabolized in the liver, and both parent compound and metabolites are excreted in the urine through glomerular filtration and active tubular secretion. Significant tubular reabsorption can occur, but it is highly pH-dependent.

Aspirin is the most effective NSAID for antiplatelet therapy, which may be beneficial in the management of equine laminitis, disseminated intravascular coagulation, and equine verminous arteritis. Aspirin irreversibly acetylates the COX in platelets. This acetylation inhibits the formation of thromboxane A<sub>2</sub>, which is responsible for vasoconstriction and platelet aggregation. A precise antiplatelet dose for horses has not been established, but a dose of 30 mg/kg every 12 hours is suggested.

#### Carprofen

Carprofen (Zenecarp) is a propionic-acid derivative formulated as a racemic mixture. Currently available for use in

horses in Europe, approval is being sought in North America. At the recommended dose of 0.7 mg/kg, carprofen has a longer elimination half-life (>15 hours) than most other NSAIDs. Similar to other NSAIDs, carprofen accumulates in inflammatory exudate but produces only modest reductions in the concentrations of eicosanoids, compared with flunixin meglumine or phenylbutazone. Despite this limitation, carprofen produces significant analgesia, likely a result of actions on the central nervous system.

### Flunixin Meglumine

Flunixin meglumine (Banamine and generic preparations) is a very potent inhibitor of COX that is approved for use in horses and is available in injectable and oral paste and granule formulations. Flunixin is rapidly absorbed after oral administration, with a bioavailability of 86% and peak serum levels achieved within 30 minutes. Although the drug is highly protein-bound, it appears to readily partition into tissues, with a relatively high volume of distribution of 0.2 L/kg. The onset of antiinflammatory action is within 2 hours, peak response occurs between 12 and 16 hours, and duration of action is 36 hours. Analgesic effects have a more rapid onset and shorter duration than antiinflammatory effects. Only 14% of a dose is excreted in urine, but little else is known about the metabolism of flunixin.

Flunixin is used in horses to treat a variety of inflammatory and painful conditions, including colic, colitis, laminitis, ocular disease, endotoxic shock, general surgery, respiratory disease, and exertional rhabdomyolysis. Flunixin is more effective at preventing the clinical signs of endotoxemia than phenylbutazone, dipyrone, and ibuprofen and may prevent abortion in endotoxic mares. The usual dose is 1.1 mg/kg every 12 hours. Low-dose therapy at 0.25 mg/kg every 8 hours has anti-endotoxic effects without masking clinical colic signs. High doses of flunixin may mask signs of surgical colic pain and interfere with treatment decisions.

Flunixin has a good safety profile, but high doses or longer durations of therapy can cause anorexia, depression, and GI ulcers. Intramuscular (IM) injections of flunixin are irritating to the muscle and have been incriminated in cases of clostridial myositis in horses, so they should be avoided when possible. If not treated promptly and aggressively, clostridial myositis can be fatal.

### Ketoprofen

Ketoprofen is a propionic-acid derivative approved for horses as a racemic solution for intravenous (IV) or IM injection (Ketofen, Anafen). Oral and rectal bioavailability is too poor to be of clinical use. Ketoprofen is highly protein-bound (92.8%), with a moderate volume of distribution for both enantiomers (0.48 L/kg) and a short plasma elimination half-life of 1 to 1.5 hours. Ketoprofen is hepatically metabolized by conjugation reactions. The usual dose is 2 mg/kg every 24 hours. The maximum antiinflammatory effects of ketoprofen occur 12 hours after dosing and last for 24 hours. Results of a number of different studies indicate that ketoprofen is at least and in some cases may be more effective than flunixin and phenylbutazone in treating pain and inflammation in horses.

Ketoprofen also appears to have a better safety profile in horses than flunixin or phenylbutazone, although very high doses can cause depression, icterus, nephritis, hepatitis, and hemorrhagic necrosis of the adrenal glands.

### Meclofenamic Acid

Meclofenamic acid (Arquel) is an oral granule used in horses for the treatment of musculoskeletal conditions. The onset of clinical action is 36 to 96 hours after administration, and significant efficacy can be seen for days. The dose is 2.2 mg/kg by mouth every 24 hours. Feeding before dosing may delay absorption of meclofenamic acid. Repeated daily dosing does not result in drug accumulation; therefore this drug is useful for chronic inflammatory conditions.

Many horses can be maintained comfortably without side effects with twice-weekly dosing. In clinical studies researchers found clinical improvement in lameness in two thirds of treated horses but found it difficult to predict which horses would respond to meclofenamic acid. At normal doses, some decrease in plasma protein concentration may be seen. Doses of six to eight times the label dose result in toxicities including weight loss, edema, mouth ulcers, depression, and anorexia. Chronic administration at the label dose to stallions and pregnant mares caused no toxic effects.

### Phenylbutazone

Phenylbutazone is the most widely used NSAID for the treatment of horses and is available in many generic IV and oral formulations. After oral administration, phenylbutazone is well absorbed but the time to its peak concentration may be delayed by feeding. The drug is distributed throughout the body, with highest concentrations in the liver, heart, kidney, lungs, and plasma. Plasma protein binding in horses is greater than 99%. Phenylbutazone and its metabolite cross the placenta and are excreted in milk. Phenylbutazone is metabolized in the liver to oxyphenbutazone, an active metabolite that is eliminated more slowly from the body than phenylbutazone. Less than 2% phenylbutazone is excreted in the urine as unchanged drug.

The capacity of the liver to metabolize phenylbutazone becomes overwhelmed at relatively low drug doses, resulting in dose-dependent kinetics. The plasma elimination half-life increases from 3 to 8 hours with increasing dose rates; high or frequent doses of phenylbutazone therefore result in disproportionately increasing plasma concentrations that can easily result in toxicity. Foals have prolonged elimination half-lives, compared with adults, most likely as a result of their immature hepatic metabolism. Therapeutic efficacy lasts for more than 24 hours because of the irreversible binding of phenylbutazone to COX and its slow elimination from inflamed tissues (with an elimination half-life of 24 hours) as well as the long plasma elimination half-life of oxyphenbutazone. Oxyphenbutazone, for example, has been detected in horse urine as long as 48 hours after a single dose. Both phenylbutazone and oxyphenbutazone induce hepatic metabolism and can affect the clearance of other hepatically metabolized drugs.

Phenylbutazone is used extensively in horses to treat a wide variety of musculoskeletal disorders. The drug is economical, and many generic brands are available. An initial dose of 4.4 mg/kg every 12 hours the first day of therapy is followed by a decreased dose and increased dosing interval for subsequent therapy. The dosage should not exceed 4 g/horse/day. Because of accumulation from the long elimination half-life of oxyphenbutazone, chronic therapy should be given every other day.

Phenylbutazone has a narrow safety margin, especially in foals, ponies, and dehydrated horses. Phenylbutazone toxicity most commonly results in GI effects, including oral, cecal, gastric, esophageal, and right dorsal colonic ulcerations, with accompanying anemia, leukopenia, hypoproteinemia, and protein-losing enteropathy. Renal papillary necrosis (renal medullary crest necrosis) occurs because of inhibition of prostaglandins that maintain renal blood flow and direct toxicity of phenylbutazone and metabolites. Phenylbutazone also may interact with other highly protein-bound drugs, such as warfarin (Coumadin). Extravascular administration results in severe tissue necrosis. Phenylbutazone significantly suppresses total  $T_4$  and free  $T_4$  concentrations in horses for 10 days.

### Vedaprofen

Vedaprofen (Quadrisol 100) is structurally related to ketoprofen and carprofen and also is formulated as a racemic

mixture. Vedaprofen is available as a palatable gel for oral administration with a loading dose of 2 mg/kg, followed by 1 mg/kg every 12 hours. Oral bioavailability is approximately 100%, and the drug is highly protein-bound (99%). In an equine acute nonimmune inflammation model, vedaprofen produced significant inhibition of inflammatory swelling and partially inhibited leukocyte migration into the exudate. Inhibition of leukocyte migration was not seen in this model with other NSAIDs. Vedaprofen was more effective than phenylbutazone in clinical trials of lameness and soft tissue injuries.

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## CHAPTER 1.4

# Slow-Acting, Disease-Modifying Drugs for Treatment of Osteoarthritis

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**T**herapy for osteoarthritis in horses may include rest, nonsteroidal antiinflammatory drugs (NSAIDs), intraarticular corticosteroids, and surgical fusion. The purported detrimental effects and marginal long-term benefits of corticosteroids, as well as the cost of surgical intervention, have led many clinicians to search for alternate means of therapy. Toward this end, the use of disease-modifying agents has become widespread. This form of therapy is directed at protecting the existing cartilage by modifying the net anabolism and catabolism of the cartilage matrix. This chapter addresses only the "slow-acting" agents hyaluronic acid (HA) and polysulfated glycosaminoglycans (PSGAGs). Optimizing the effects of such

agents requires some level of understanding of the pathophysiology of synovitis and arthritis.

Determining as closely as possible the underlying cause of joint disease, the intraarticular structures involved, and the stage of the disease should constitute the goals of clinical examination. Typically, the more reactive a tissue, the more rapidly it responds to treatment. The more rapidly the disease process can be brought under control and the intraarticular homeostasis returned to normal, the less significant the long-term sequelae will be. With this generalization in mind, it is possible to rank the reactivity of the tissues involved in synovitis/arthritis. The most responsive tissues in the joint are the vasculature, followed



Phenylbutazone is used extensively in horses to treat a wide variety of musculoskeletal disorders. The drug is economical, and many generic brands are available. An initial dose of 4.4 mg/kg every 12 hours the first day of therapy is followed by a decreased dose and increased dosing interval for subsequent therapy. The dosage should not exceed 4 g/horse/day. Because of accumulation from the long elimination half-life of oxyphenbutazone, chronic therapy should be given every other day.

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### Vedaprofen

Vedaprofen (Quadrisol 100) is structurally related to ketoprofen and carprofen and also is formulated as a racemic

mixture. Vedaprofen is available as a palatable gel for oral administration with a loading dose of 2 mg/kg, followed by 1 mg/kg every 12 hours. Oral bioavailability is approximately 100%, and the drug is highly protein-bound (99%). In an equine acute nonimmune inflammation model, vedaprofen produced significant inhibition of inflammatory swelling and partially inhibited leukocyte migration into the exudate. Inhibition of leukocyte migration was not seen in this model with other NSAIDs. Vedaprofen was more effective than phenylbutazone in clinical trials of lameness and soft tissue injuries.

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## CHAPTER 1.4

# Slow-Acting, Disease-Modifying Drugs for Treatment of Osteoarthritis

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Therapy for osteoarthritis in horses may include rest, nonsteroidal antiinflammatory drugs (NSAIDs), intraarticular corticosteroids, and surgical fusion. The purported detrimental effects and marginal long-term benefits of corticosteroids, as well as the cost of surgical intervention, have led many clinicians to search for alternate means of therapy. Toward this end, the use of disease-modifying agents has become widespread. This form of therapy is directed at protecting the existing cartilage by modifying the net anabolism and catabolism of the cartilage matrix. This chapter addresses only the "slow-acting" agents hyaluronic acid (HA) and polysulfated glycosaminoglycans (PSGAGs). Optimizing the effects of such

agents requires some level of understanding of the pathophysiology of synovitis and arthritis.

Determining as closely as possible the underlying cause of joint disease, the intraarticular structures involved, and the stage of the disease should constitute the goals of clinical examination. Typically, the more reactive a tissue, the more rapidly it responds to treatment. The more rapidly the disease process can be brought under control and the intraarticular homeostasis returned to normal, the less significant the long-term sequelae will be. With this generalization in mind, it is possible to rank the reactivity of the tissues involved in synovitis/arthritis. The most responsive tissues in the joint are the vasculature, followed

by the synovial intima, subintima, cartilage, and subchondral bone. Although in rare instances only one of these structures is involved, it is useful to attempt to characterize the major changes in the individual tissues associated with the disease process. Slow-acting, disease-modifying agents (SADMOAs) are used to reduce the destructive effects of inflammatory mediators released by the inflamed synovium and, if possible, return articular cartilage to a more normal remodeling process.

## HYALURONIC ACID

Hyaluronic acid is the most widely used intraarticular medication in horses. The selection of this medication, and the route by which it is administered, is often decided on without consideration of the underlying disease process or the limitations of HA therapy. Naturally occurring HA is a relatively ubiquitous molecule in mammals that is produced by a membrane-bound enzyme—hyaluronan synthase. The HA present in synovial fluid is often said to be produced by fibroblastic synoviocytes. Recently, however, researchers have demonstrated that at least three isoforms of hyaluronan synthase exist and that the enzymes are expressed in cell culture by synovial cells, chondrocytes, and osteosarcoma cell lines. HA itself is a relatively simple molecule of repeating disaccharide units and has a variety of effects once extruded into the extracellular matrix. For example, HA confers compressive strength to the articular cartilage when functioning as the core molecule for proteoglycan aggregates. It also imparts viscoelasticity to the synovial fluid and functions as a restrictive barrier to molecules threatening to enter the joint proper.

Although the actions of naturally occurring HA are fairly well-characterized, determining the beneficial effects of the exogenous products has proven elusive. In the clinical setting, prolonged benefit from treatment with HA is observed in the form of reduced joint effusion and severity of lameness. This prolonged benefit is highly unusual for a product that has a half-life in the synovial space on the order of several hours. In an acute inflammatory process the theory is that at least one possible beneficial mechanism is the return of the steric barrier provided by HA. In support of this theory, HA has been shown to have a protective effect against the margination and diapedesis of polymorphonuclear cells and lymphocytes. However, this effect has been documented to occur only with the use of the higher-molecular-weight forms. The actual mechanism of this effect has yet to be elucidated, but some evidence exists that it is related to cellular interactions with the CD44 molecule. Other possible antiinflammatory benefits have been difficult to confirm. For example, the purported induction of endogenous HA production and the reduction in matrix metalloproteases have been refuted in some studies. Nonetheless, it does seem that the intraarticular administration of HA reduces inflammation by modulating the production of inflammatory mediators, such as prostaglandins, specifically PGE<sub>2</sub>.

Extensive research has also been undertaken to determine HA's possible anabolic and anticatabolic effects on articular cartilage. For example, in a cast-confinement model, HA was shown to minimize cartilage degeneration.

This chondro-stabilizing influence on articular cartilage has been proposed as a manifestation of HA-induced down-regulation of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ).

## Therapeutic Use of Hyaluronic Acid

As a therapeutic agent, HA is best suited for acute inflammatory conditions, where its ability to reduce the influx of white blood cells into the joint space could modify the disease process by decreasing the subsequent steps in the inflammatory cascade. Therefore a defined condition of pure synovitis would be the most amenable to treatment with HA. Such a condition is rarely found in the clinical setting, as most of the conditions treated in the equine athlete involve some degree of underlying cartilage degeneration. In these conditions HA might still reduce the rate of degeneration without contributing to the catabolic process already under way in the articular cartilage.

However, HA has little ability to eliminate severe forms of lameness. In addition, in a joint with overwhelming inflammation—in which HA is rapidly broken down to its low-molecular-weight fragments—it might even have deleterious effects. Low-molecular-weight fragments have the potential to increase inflammation by inducing neovascularization and increasing white cell influx and metalloprotease formation. Therefore with marked inflammatory conditions the use of HA is recommended in conjunction with intraarticular corticosteroids or alternatively with adjunct therapy in the form of restricted exercise and NSAIDs. When HA is used as a protective medication in conjunction with corticosteroids, the use of one of the lower-cost, low-molecular-weight forms may be adequate. Most clinicians opt to use the highest-molecular-weight form available when using HA as a stand-alone therapy, although this practice has recently been brought under question.

HA also is commonly used in the postoperative period. In this situation the timing of HA administration is a combination of personal preference and understanding of the disease process in question. This author most commonly uses stall confinement and NSAIDs in the immediate postoperative period to begin confronting the inflammation and subsequently uses HA 2, 4, and 6 weeks after surgery in an attempt to normalize the healing intraarticular environment. If the joint has marked cartilaginous lesions or proliferative synovitis, corticosteroids are administered with the HA 4 and 6 weeks after surgery.

Clients should be made aware of the potential for complications after HA injections, including hemarthrosis, immune-mediated flares, and infection. Development of iatrogenic hemarthrosis generally occurs shortly after the injection, with the horse potentially developing a grade 5/5 lameness. The severity of the lameness depends on the type of joint, along with the rate and volume of blood entering the joint. Sepsis in joints medicated with HA alone usually develops within 12 to 24 hours of the injection. The flare associated with the instillation of the foreign protein can also develop during this same time period. As a generalization the flare response induces a lower degree of lameness (grade 3-4/5), although the amount of edema and palpable heat in the affected limb can be profound. Treatment of hemarthrosis requires lavage of the joint and

firm pressure wraps to stop the bleeding and relieve the pain. Flares are controlled effectively with the use of a systemic trichlormethiazide-dexamethasone combination (Naquasone) and topical cataplasms. Treatment of infections secondary to joint injections should always be aggressive with joint lavage, systemic and local antibiotics, NSAIDs, and rest.

## POLYSULFATED GLYCOSAMINOGLYCANS

Polysulfated glycosaminoglycans (Adequan) are routinely used in veterinary medicine to treat various forms of arthritis. Adequan is a synthetic heparinoid made by esterification of fractions from bovine lung and trachea. The major component in this admixture of glycosaminoglycans is chondroitin sulfate. Adequan is commonly administered either intramuscularly or intraarticularly.

PSGAGs have a number of possible sites of action in the treatment of arthritis, but the exact mechanisms of action have not been determined. In any attempt to decipher the net effects of Adequan, it is necessary once again to consider the reactivity of the component tissues in the joint. For example, one of the most consistent results of PSGAGs in various inflammatory models has been the reduction of edema formation. In studies this reduction occurred regardless of whether the compounds were administered before or after the development of edema. The mechanism for this effect of PSGAGs was hypothesized as a decrease in the permeability of the microvasculature. PSGAGs also have been shown to help reduce the diapedesis of leukocytes into a site of inflammation. In addition, evidence exists that PSGAGs can reduce the production and effects of prostaglandins, matrix metalloproteases, interleukin-1 (IL-1), and TNF- $\alpha$ . Multiple studies have demonstrated the beneficial effects of a reduction in the production of destructive enzymes. Once the effects of the inflammatory process have begun to affect the articular cartilage, however, a greater duration of treatment will be required before beneficial effects may be seen.

Disease modification requires not only the reduction of the catabolic effects of the disease, but also the anabolism of healing. Halting the inflammatory changes is necessary before the matrix can be rebuilt to return the joint to normality. PSGAGs have been shown to increase the degree of polymerization of HA in the joint, improve the net rheologic properties of the joint fluid, reduce the detrimental effects of intraarticular corticosteroids, and decrease the proteoglycan depletion that occurs during cast immobilization. The exact mechanisms of action for the anabolic effects of PSGAGs have yet to be determined.

### Therapeutic Use of Polysulfated Glycosaminoglycans

The protocol for administration of Adequan varies with respect to the condition being addressed. For example, when the medication is used as a protective agent for cast-

associated cartilage protection, it is administered weekly during the entire period of cast confinement and for 4 weeks after cast removal. In contrast, as an adjunct therapy during the administration of corticosteroids, the timing and duration depends on the steroid being administered. In these situations the clinician should consult a reference on the duration of the catabolic effects associated with the individual steroid in question. When Adequan is used postoperatively as a component in the anti-inflammatory milieu, the condition under treatment must be taken into consideration. For example, acute osteochondral fragments rarely require Adequan therapy to return the animal to work.

In the event that the owner or trainer requests Adequan, one intramuscular (IM) injection is generally administered weekly for 4 weeks, after which treatment is discontinued unless effusion or pain on manipulation persists. Modifications of this therapy are based on intraoperative findings and clinical examinations during the rehabilitation period. In serious cases, Adequan may be required at each step in the rehabilitation process to reduce the rate of degeneration in the remaining cartilage. This author typically attempts to wean the patient from the medication once full work has been achieved, encouraging the owner/trainers to resume its use only during times of increased work stress. Many animals appear to develop a tolerance to the effects of Adequan if they are maintained on constant therapy for 6 months or more.

Joint infections are the most common complication seen with the intraarticular route of administration for Adequan. For this reason many clinicians have elected to add amikacin to the injection, if not to completely eliminate this route of administration in favor of IM injections. No reports of systemic or intraarticular bleeding emergencies have been reported with the use of PSGAGs in horses, although changes in clotting parameters have been reported in dogs.

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## CHAPTER 1.5

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# Injectable Anesthetic Protocols

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To facilitate the performance of short diagnostic, therapeutic, or surgical procedures in the horse, clinicians often induce recumbency with injectable anesthetic drugs. The clinician must achieve an adequate plane of anesthesia and analgesia to facilitate these manipulations, while minimizing the complications associated with drug-induced recumbency. Induction to and recovery from anesthesia should be smooth, and the duration of recumbency should be consistent. Because no single anesthetic drug meets these requirements, however, a combination of drugs is frequently used. This chapter provides a brief review of contemporary techniques for short-term injectable anesthesia for horses. The reader is encouraged to use the information in this chapter to select the drug combinations most suited to the horse, the working conditions/situation, and the procedure to be performed. Knowledge of the pertinent advantages and disadvantages of the drugs, used individually and in combination, is the key to ensure a positive outcome.

### SEDATIVES AND TRANQUILIZERS

Adequate sedation before the induction of anesthesia is key to achieve a smooth transition to lateral recumbency.  $\alpha_2$ -Adrenergic agonist drugs (e.g., xylazine, detomidine) have largely replaced phenothiazine tranquilizers (e.g., acepromazine, chlorpromazine) because of their action as sedative-analgesics.  $\alpha_2$ -Adrenergic agonist drugs also have muscle-relaxant properties and counter the muscle hypertonicity associated with many anesthetic induction agents. These desirable  $\alpha_2$ -adrenoceptor agonist actions are mediated largely by the inhibition of the release of excitatory neurotransmitters, such as norepinephrine. However, this inhibition is also associated with a decrease in sympathetic tone, which may contribute to bradycardia, bradydysrhythmias, and hypotension. Hypotension usually follows an initial period of drug-vascular receptor-mediated hypertension. Other clinically relevant effects, such as a decrease in gastrointestinal (GI) motility and an increase in urine output, are mediated by drug actions on other receptor sites (e.g., inhibition of antidiuretic hormone).

Drug affinity for the  $\alpha_2$ -adrenoceptor determines the duration of both desirable and undesirable effects. Xylazine has the lowest receptor affinity, highest dose requirement, and shortest duration of action of the clinically available  $\alpha_2$ -adrenergic agonists. Detomidine and romifidine are more potent than xylazine, having a much lower effective dose and a longer duration of action.

Xylazine (as much as 1 mg/kg IV) is widely used as a sedative and preinduction agent in the horse and provides sedation within 3 to 5 minutes of intravenous (IV) administration. Sedative effects are observed for approximately 20 minutes. Intramuscular (IM) administration with a dose of 1 to 2 mg/kg may be used to facilitate handling in fractious horses, with sedative effects lasting as long as 1 hour. Xylazine-induced analgesia is commonly thought to be more pronounced in the head and cranial extremities than in the caudal regions of the body. Clinicians should use caution when working around the hind end of the animal because sudden, rapid hind limb movement (colloquially referred to as a *phantom kick*) can occur in horses sedated with xylazine.

Detomidine (as much as 20  $\mu$ g/kg IV or as much as 40  $\mu$ g/kg IM) is also used before anesthetic induction with a variety of agents. After IV administration the peak sedative action is reported to be anywhere from 5 to 20 minutes. Sedative and muscle-relaxant effects last as long as 90 minutes and may contribute to ataxia and influence the quality of recovery from anesthesia. Bradycardia and bradydysrhythmias are more pronounced with detomidine as compared with xylazine.

Romifidine, a newer and more potent  $\alpha_2$ -adrenergic agonist developed for use in horses, is also used for sedation before anesthesia with the dissociative agents. As with detomidine, prolonged sedation can occur, but associated ataxia is believed to be of a lesser magnitude.

Under circumstances in which  $\alpha_2$ -adrenergic agonist drugs do not provide adequate sedation, they may be combined with other drugs. Phenothiazine tranquilizers (e.g., acepromazine [0.01-0.03 mg/kg IV or IM]), although infrequently used alone to provide tranquilization before anesthetic induction, are occasionally combined with  $\alpha_2$ -adrenergic agonists. In addition to acepromazine's tranquilizing effect, a potentially beneficial antiarrhythmic effect is reported when this drug is combined with potent  $\alpha_2$ -adrenergic drugs. Hypotension is the most frequently observed side effect associated with acepromazine.

Phenothiazine tranquilizers and  $\alpha_2$ -adrenergic agonists also often are combined with opioid drugs in the hope of providing more reliable drug-mediated restraint than that provided by the phenothiazines or  $\alpha_2$ -adrenergic agonists alone. The other potential benefit, albeit still under investigation, is that opioid drugs may provide analgesia for horses as well as for dogs and humans. Although many opioid drugs, including fentanyl, methadone, and meperidine, may be used, butorphanol (0.02-0.04 mg/kg IV or

IM) and morphine (0.03-0.06 mg/kg IV or IM) are the most commonly administered. These drugs are usually given in addition to sedative or tranquilizing drugs because they cause excitatory behaviors (e.g., pacing and snatching at food) when administered alone to horses. GI ileus and changes in respiratory function are also reported with opiate administration to horses. These drugs are controlled, and accurate records must be kept of their use.

## DRUGS FOR ANESTHESIA INDUCTION

Although thiobarbiturates (e.g., thiopental) are still used for anesthetic induction before maintenance with inhalation anesthetics, they have been largely replaced in injectable anesthetic techniques by dissociative drugs (e.g., ketamine). This change is a result of the unpredictable quality of anesthetic induction and recovery with thiobarbiturates and the needs for special drug storage and handling procedures.

Dissociative anesthetic drugs produce a cataleptic state by interrupting ascending transmission from the unconscious to the conscious parts of the brain. Skeletal muscle movement and hypertonia occur to varying degrees. Because ketamine often causes increased muscle tone, sedative agents such as xylazine are typically administered before anesthetic induction (Table 1.5-1). After ketamine administration (2 mg/kg IV) the onset of action is fairly rapid, with a smooth transition to lateral recumbency complete in 45 seconds to 2 minutes. Anesthetic drug-induced recumbency lasts approximately 15 to 20 minutes, but repeat administration of both drugs may be used to safely extend the duration of anesthesia for approximately 1 hour.

Telazol is a combination of the longer-acting, more potent, dissociative agent tiletamine and the benzodiazepine zolazepam, which has been used in combination with xylazine and detomidine in horses (see Table 1.5-1). Prolonged and rough recoveries have been reported with xylazine and Telazol in a wide range of equids. Clinicians can achieve smoother recoveries in horses by combining butorphanol with xylazine or by using detomidine before Telazol induction. If detomidine and Telazol are used, the duration of anesthesia lasts approximately 30 to 40 minutes—that is, longer than with xylazine-ketamine.

Heart rate usually increases after administration of a dissociative drug. This increase offsets the bradycardia caused by the  $\alpha_2$ -agonists. Mean arterial pressure ranges from approximately 80 to 160 mm Hg in horses induced with these drug combinations, but cardiac output may be decreased. An irregular and apneustic respiratory pattern characterized by a pause after inspiration is common. As the animal begins to get lighter during drug-induced recumbency, respiration becomes more regular and forceful. Evaluating this change in respiratory pattern may be more useful to the clinician who is assessing anesthetic depth than to one who is monitoring eyelid reflexes, which are often maintained after dissociative drug administration.

Propofol is another induction agent that has recently been evaluated for use in horses (see Table 1.5-1). As with thiopental, unpredictable anesthetic inductions are associated with propofol use in the horse. Although induction quality can be modified with the use of sedative and muscle-relaxant drugs, cost and storage issues still limit its use. An advantage of propofol over both thiopental and ketamine is that because of its unique pharmacokinetic profile, propofol can be used to maintain anesthesia in horses

Table 1.5-1

**Selected Injectable Techniques for Induction and Short-Term Maintenance of Anesthesia in Healthy Adult Horses**

Drug	Dose (mg/kg)	Route	Duration of Recumbency (Minutes)	Associated Features	Suggested Techniques to Prolong Duration of Recumbency
xylazine	1 (2)	IV (IM)	15-20	Muscular and reflex activity present	½ to ⅓ the induction dose of each drug; triple drip to effect
ketamine	2	IV			
xylazine	0.6-1 (1-2)	IV (IM)	15-30	Smooth transition to lateral recumbency	½ to ⅓ the induction dose of each drug; triple drip to effect
diazepam	0.02-0.1	IV			
ketamine	2	IV			
xylazine	0.3-0.5 (1-2)	IV (IM)	20-30	Prolonged ataxia during induction	Additional xylazine and ketamine; triple drip to effect (not to exceed 200 mg/kg of guaifenesin)
guaifenesin	25-100	IV			
ketamine	2	IV		IV catheter recommended	
detomidine	0.02	IV	30-40	Ataxia possibly observed during recovery	
Telazol	1-2	IV			
xylazine	0.5	IV	15-20	IV catheter recommended; cost of drug possibly limiting use	Additional xylazine and propofol as bolus or by constant rate infusion (0.035 mg/kg/min xylazine and 0.1 mg/kg/min propofol)
guaifenesin	50-100	IV			
propofol	2	IV			

without significantly prolonging the duration of the recovery phase. Furthermore, the quality of recovery from anesthesia is usually excellent, with horses recovering from the influence of propofol making a single coordinated attempt to stand. Respiratory depression, as evidenced by a decrease in respiratory rate, an increase in partial pressure of carbon dioxide in arterial blood ( $\text{PaCO}_2$ ), and a decrease in partial pressure of arterial oxygen ( $\text{PaO}_2$ ) is seen especially at deep planes of anesthesia induced with propofol.

## MUSCLE RELAXANTS

Centrally acting muscle relaxants (e.g., guaifenesin, diazepam) are used to improve skeletal muscle relaxation and/or to prolong the anesthetic recumbency with the aforementioned techniques. Guaifenesin acts at interneurons in the spinal cord, whereas diazepam mediates its actions through  $\gamma$ -aminobutyric acid receptors in the brain. Cardiopulmonary effects of both drugs are negligible, and neither drug offers any analgesic benefit.

Guaifenesin (25-100 mg/kg IV) is infused to effect (i.e., profound muscle relaxation) during anesthetic induction. The concentration of the guaifenesin solution should be less than or equal to 10% to minimize hemolysis. Accidental perivascular injection should be treated to prevent regional tissue necrosis and sloughing. The addition of guaifenesin to the induction protocol allows a reduction in the dose of the sedative or induction agent and may decrease drug-related side effects. A combination of guaifenesin (50-100 mg/kg), an  $\alpha_2$ -adrenergic agonist (e.g., xylazine [1 mg/kg]) and ketamine (1-2 mg/kg), which is

often referred to as a *triple drip*, is commonly used to maintain anesthesia for procedures lasting 45 to 60 minutes. Although this combination is effective, clinicians must take caution to prevent overdose in animals. Guaifenesin toxicity occurs at a dose of approximately 200 mg/kg. Unfortunately early toxicity manifests as an increase in muscle rigidity and is often misdiagnosed and treated with additional guaifenesin, which can result in respiratory and subsequent cardiac arrest.

Like guaifenesin, diazepam (0.02-0.1 mg/kg IV) is used to smooth the anesthetic induction and reduce the dose of concurrently administered drugs. The injection volume is small and allows for diazepam to be combined in the syringe with ketamine for anesthetic induction. Transient respiratory depression is more common when diazepam is used during anesthetic induction. Because diazepam is a controlled substance, accurate records for its use must be maintained.

## Supplemental Readings

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## CHAPTER 1.6

# Critical Care Therapeutics for Mature Horses

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Critical care facilities are becoming commonplace in referral and university veterinary hospitals, and many of these facilities are able to offer intensive treatment and monitoring of horses. Many such patients are suffering from gastrointestinal (GI) disease; however, any horse in need of rigorous monitoring and/or intravenous (IV) fluid therapy may benefit from stabilization in the intensive care environment. In addition to meeting the fluid requirements and balancing the acid-base and electrolyte status of these horses, clinicians often must administer analgesics, antiendotoxic therapeutics, and antiinflammatories—supportive care that can significantly reduce patient morbidity and mortality. This chapter provides an

overview of common therapeutics used to treat mature horses in the critical care setting.

## ANTIINFLAMMATORIES

### Nonsteroidal Antiinflammatory Drugs

Nonsteroidal antiinflammatory drugs (NSAIDs) are commonly used for their analgesic, antipyretic, antiinflammatory, antithrombotic, and antiendotoxic properties (see Chapter 1.3: "Nonsteroidal Antiinflammatory Drugs"). Well-documented toxicities associated with these drugs include gastric and right dorsal colon ulceration and renal

without significantly prolonging the duration of the recovery phase. Furthermore, the quality of recovery from anesthesia is usually excellent, with horses recovering from the influence of propofol making a single coordinated attempt to stand. Respiratory depression, as evidenced by a decrease in respiratory rate, an increase in partial pressure of carbon dioxide in arterial blood ( $\text{PaCO}_2$ ), and a decrease in partial pressure of arterial oxygen ( $\text{PaO}_2$ ) is seen especially at deep planes of anesthesia induced with propofol.

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## ANTIINFLAMMATORIES

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Nonsteroidal antiinflammatory drugs (NSAIDs) are commonly used for their analgesic, antipyretic, antiinflammatory, antithrombotic, and antiendotoxic properties (see Chapter 1.3: "Nonsteroidal Antiinflammatory Drugs"). Well-documented toxicities associated with these drugs include gastric and right dorsal colon ulceration and renal

crest necrosis. Less-recognized adverse effects include the potential for delays in cortical bone healing and decreased large colon motility. NSAIDs must be used judiciously and in well-hydrated animals, and the animal should be monitored routinely for clinical signs of toxicity. Flunixin meglumine (0.25 mg/kg IV PO q8h to 1.1 mg/kg IV PO q12h) is commonly chosen for soft-tissue-related problems, including GI insults. Flunixin is also labeled for the intramuscular (IM) route, but this author has seen some serious injection site abscesses after IM administration and prefers to avoid this route. Phenylbutazone (2.2-4.4 mg/kg IV/PO q12h) is purported to be a superior drug for musculoskeletal problems. Some evidence exists that ketoprofen (1.1-2.2 mg/kg IV/IM q12h) may result in fewer side effects such as gastric ulceration.

### Corticosteroids

Corticosteroids have antiinflammatory activity mediated by the inhibition of the cyclooxygenase (COX) and lipoxygenase pathways. The potential for corticosteroids to depress immune function, as well as the association between certain corticosteroids and the development of laminitis, limits their clinical use in some circumstances. This author does not commonly use steroids in the intensive care setting with the exception of treating immune reactions, including anaphylaxis and hypersensitivity reactions.

### Dimethyl Sulfoxide

Dimethyl sulfoxide (DMSO) is a liquid solvent with purported antimicrobial, analgesic, antiinflammatory, and free radical scavenging properties. DMSO blocks the synthesis of prostaglandins and scavenges hydroxyl radicals. Its systemic use (as much as 1 g/kg diluted with 0.9% saline to <10% solution, slowly IV) is reported for use in horses with neurologic disease and reperfusion injury and as a diuretic. Rapid IV administration of greater than 10% solutions can result in hemolysis. DMSO is only licensed for use as a topical antiinflammatory in animals.

## ANALGESICS

### Opioids

Opioids such as morphine and butorphanol can induce profound analgesia in horses. The use of morphine (0.02-0.04 mg/kg IV or 0.22 mg/kg IM) or butorphanol (0.02-0.1 mg/kg IV/IM) alone, however, usually results in excitement. To avoid this undesirable effect, opioids should be used in combination with other sedatives/analgesics, such as  $\alpha_2$ -adrenergic agonists. Most opioids exacerbate respiratory depression, although this is not a common concern in adult horses. Because morphine is a pure  $\mu$ -opioid receptor agonist and butorphanol is a mixed  $\kappa$ -agonist and  $\mu$ -antagonist, morphine and butorphanol should not be used together. Opioids, most commonly morphine, can also be used in the epidural space to provide longer-lasting analgesia of the perineal region and hind limbs. Onset and duration of analgesia varies with the drug, the volume injected, and the site of injection; onset of action can range from 20 minutes to more than 4 hours, and duration of ac-

tion can range from 8 to 19 hours. This author typically injects 0.1 to 0.2 mg/kg morphine diluted to a total volume of 12 ml in the caudal epidural space. If used in combination with an  $\alpha_2$ -adrenergic agonist (xylazine 0.1 mg/kg), the morphine dose is decreased to a maximum of 0.1 mg/kg.

Fentanyl, a  $\mu$ -opioid agonist, can be administered through transdermal patches in small animals to provide long-term, potent analgesia. Although only approved for use in dogs, fentanyl transdermal patches (Duragesic) can be adapted for use in horses. Two 10-mg patches, which are designed to release 100  $\mu$ g/hour, would be appropriate for a 450-kg horse. The onset of analgesia after the placement of a fentanyl patch is delayed, usually from 12 to 24 hours, and duration of analgesia is reported to last as long as 48 hours after onset. Clinical trials are currently in progress to document the pharmacokinetics and potential side effects of transdermal fentanyl administration in horses.

### $\alpha_2$ -Adrenergic Agonists

These drugs, including xylazine (0.3-0.5 mg/kg IV/IM) and detomidine (20-40  $\mu$ g/kg IV/IM), can provide analgesia in addition to sedation, especially when used in combination with opioids.  $\alpha_2$ -Adrenergic agonists significantly reduce GI motility and therefore should be used judiciously in horses with GI disorders. When used in the caudal epidural space,  $\alpha_2$ -adrenergic agonists (xylazine 0.17 mg/kg; detomidine 15-30  $\mu$ g/kg) can also provide analgesia. This author frequently combines xylazine with morphine in the caudal epidural space (see previous discussion of opioids for dosages).

### Local Anesthetics

Local anesthetic agents (lidocaine or mepivacaine hydrochloride, 2%) can afford analgesia if administered into the caudal epidural space. The extent of analgesia depends on the volume injected. Adequate desensitization of the urethra, bladder, and perineal and anal regions, in addition to the relief of tenesmus, usually occurs after the administration of 6 ml of 2% lidocaine (0.26 mg/kg) into the caudal epidural space of a 450-kg horse. Injection of large volumes of fluid into the caudal epidural space may result in ataxia and even recumbency, and injection of more than 10- to 15-ml volumes is not recommended. This author has infrequently noted ataxia and recumbency with volumes as small as 5 ml of a 2% solution. In addition, some evidence exists that lidocaine, when used as a prokinetic at a constant IV infusion of 0.05 mg/kg/min, has generalized analgesic properties.

## ANTIMICROBIALS

A comprehensive discussion of antimicrobials can be found in Chapter 1.2: "Antimicrobial Therapy for Horses." Broad-spectrum antimicrobials are commonly incorporated into the perioperative and postoperative management of adult equine patients. Some hospitals frequently include an aminoglycoside such as gentamicin as well as either a penicillin derivative or a cephalosporin. Antibio-



otics should be chosen with the patient's clinical disease, systemic state, and applicable microbiologic culture and sensitivity results in mind. In most university and referral practices, therapeutic drug monitoring is available and should be taken advantage of when indicated.

## DRUGS TO COMBAT ENDOTOXIN

Endotoxemia complicates the clinical picture in many disease states in horses, including GI insults and other gram-negative bacteremic events. Circulating endotoxins result in the stimulation of several endogenous mediators. Clinicians must address the primary problem to manage horses in endotoxic shock; however, therapeutic agents are available that help stabilize horses suffering from endotoxemia.

### Nonsteroidal Antiinflammatory Drugs

NSAIDs, in particular flunixin meglumine (0.25 mg/kg IV PO q8h to 1.1 mg/kg IV PO q12h), remain the most common drugs given for the clinical signs of endotoxemia in horses. NSAIDs have no direct actions against the endotoxin molecule, and their therapeutic benefits are believed to be mediated through the inhibition of prostanoid production, one of the end products of the COX pathway.

### Polymyxin B

The antibiotic polymyxin B binds the lipid-A moiety of the circulating endotoxin molecule, likely a result of its detergent properties. The recommended dose of polymyxin B (1000-6000 U/kg q12h in 1 L 0.9% saline IV during a 30-minute period) is much lower than the antimicrobial dose used in other species. Polymyxin B is nephrotoxic and neurotoxic; its use only in well-hydrated horses with normal renal parameters is critical. Animals must be monitored closely for signs of toxicosis, such as azotemia, proteinuria, and/or ataxia.

### Pentoxifylline

Pentoxifylline (Trental), a methylxanthine derivative, has rheologic properties that increase erythrocyte deformability and decrease platelet aggregation. This drug also has reputed actions against cytokines, such as tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-1, IL-6, and thromboplastin. *In vivo* studies have suggested that pentoxifylline has limited clinical efficacy when administered alone after endotoxin challenge in horses. When administered simultaneously with flunixin meglumine, the antiendotoxic effects of pentoxifylline appear to be slightly improved. The dose is 7.5 mg/kg IV by mouth every 12 hours. Pentoxifylline may be teratogenic at high doses.

### Hyperimmune Serum

Immunization to conserved epitopes of the lipid-A moiety of lipopolysaccharide theoretically imparts protection against the clinical signs associated with endotoxemia. The use of antiendotoxin plasma products, including Endoserum (Immvac, Columbia, Mo.) and Equine J-5 Plasma

(Veterinary Dynamics, San Luis Obispo, Calif.) is controversial because clinical trials of the efficacy of these products have reported mixed results. As with any such protein products, hypersensitivity reactions are possible. The cost of these treatments can also be considerable. Clinicians should administer 1.5 ml/kg IV slowly during a 45- to 60-minute period and monitor the animal closely for adverse reactions.

## PROKINETIC AGENTS

Horses with acute abdominal crises, especially lesions involving the small intestine, are at substantial risk for developing ileus and may require prokinetic therapy to encourage restoration of normal GI motility patterns. A number of prokinetic agents are available, and factors such as the site of obstruction or motility disturbance and potential drug side effects help the clinician to determine the most suitable prokinetic (Table 1.6-1).

## HEMOSTATIC AGENTS

Horses with uncontrolled hemorrhage that are not candidates for surgical intervention can benefit from therapeutics that potentially accelerate the hemostatic process. The following therapeutics may be used in conjunction with other therapies designed to stabilize a patient in hemorrhagic shock.

Derivatives of the amino acid lysine, including aminocaproic acid (Aminocaproic Acid USP Injection) are antifibrinolytic drugs by virtue of their ability to irreversibly bind to plasminogen and subsequently inhibit tissue fibrinolysis. The loading dose of aminocaproic acid is 20 g in 5 L lactated Ringer's solution administered intravenously during a 30- to 60-minute period and followed by 10 g aminocaproic acid in 5 L lactated Ringer's solution administered intravenously during a 30- to 60-minute period four times daily.

Ergonovine maleate is thought to be valuable in situations involving uterine artery/broad ligament hemorrhage because ergonovine vasoconstricts and mildly contracts the uterus. Some clinicians have expressed concern, however, that uterine contraction may exacerbate a broad ligament hemorrhage. For a 450-kg horse, clinicians should administer 3 to 5 mg IM every 4 hours.

Conjugated estrogens (Primarin) are reported to shorten prolonged bleeding times in humans; however, the mechanism of action is unknown. In humans, conjugated estrogens are considered to have a significantly longer duration of action than the lysine derivatives. The recommended dose in a 45-kg horse is 50 mg IV administered once.

Formalin (10%) when administered intravenously is hypothesized to coagulate proteins that may accelerate a hemostatic clot. The clinical efficacy of formalin is predominantly anecdotal, and controlled clinical studies in healthy horses at dosages not associated with side effects have failed to show significant alterations in hemostatic function. The reported dose is 30 ml of a 10% formalin solution in 5 L of lactated Ringer's solution administered intravenously during a 30- to 60-minute period.

Endogenous opioids released during a hemorrhagic crisis can negatively affect cardiovascular parameters. Naloxone hydrochloride is alleged to reduce these potentially

**Table 1.6-1**  
**Prokinetic Drugs Used for the Treatment of Ileus in Horses**

Prokinetic	Mechanism of Action	Site of Action	Side Effects	Contraindications	Dose
lidocaine (2%)	Reduces circulating catecholamines; stimulates smooth muscle; decreases prostaglandin synthesis, analgesia; suppresses primary afferent neurons	Small intestine, large colon	Cardiac arrhythmia, ataxia, muscle tremors, collapse	Sepsis: interferes with granulocyte migration and retards bacterial killing <i>in vitro</i>	Initially 1.3 mg/kg IV slowly then 0.05 mg/kg/min in 0.9% saline during a 24-hr period
cisapride	Antagonizes inhibitory effects of 5-OH-tryptamine; increases acetylcholine release at myenteric plexus	Esophagus, stomach, small intestine, large and small colon	None reported	Gastric/small intestine reflux: interferes with oral absorption <ul style="list-style-type: none"> <li>• No IV/IM product available</li> <li>• Not reliably absorbed per rectum</li> </ul>	0.1 mg/kg PO q8h
erythromycin lactobionate	Motilin agonist	Stomach, pelvic flexure, cecum, ileum	Colic, diarrhea	Adverse reactions	1.0-2.2 mg/kg in 1 L 0.9% saline IV during a 45-minute period q6h
metoclopramide	Dopamine antagonist; serotonin agonist leads to increase in acetylcholine at neuromuscular junction	Stomach, small intestine	Extrapyramidal (colic, ataxia, excitement)	Adverse reactions	0.1-0.25 mg/kg in 500 ml 0.9% saline IV during a 30- to 60-minute period q8h/q6h
neostigmine methylsulfate	Acetylcholinesterase inhibitor	Cecum, large colon	Colic	Strangulating obstructions	0.0044-0.022 mg/kg SQ/IV q20min; not to exceed 10 mg/450 kg

PO, By mouth; q8h, every 8 hours; IV, intravenous; SQ, subcutaneous.

harmful effects at a dose of 5 to 8 mg administered intravenously once.

A transfusion with blood-replacement products should be considered if the total plasma protein is below 3 mg/dl, the hematocrit is less than 15, or the patient appears to be clinically unstable or deteriorating. In this situation, if a compatible donor is accessible, a whole-blood transfusion (20 ml/kg/hr) is ideal. If cross-matching capabilities or a universal blood donor is unavailable, a plasma transfusion (10 ml/kg/hr) may provide necessary clotting factors and platelets, as well as colloid properties.

## MEDICATIONS FOR ULCERS

Hospitalized horses are at risk of developing gastric ulcers, which can complicate the clinical picture and may be associated with the primary disease or associated with stress or alterations in diet and exercise habits. Ulcers may also

be drug-induced, in particular after chronic use of NSAIDs. Enteric-coated omeprazole (treatment 4 mg/kg PO q24h; prevention 2 mg/kg PO q24h), a substituted benzimidazole that inhibits the gastric proton pump, has been shown to be effective in the treatment and prevention of gastric ulcers. Omeprazole is currently available only in an oral formulation. If the oral route of administration is not feasible, alternatives such as histamine<sub>2</sub>-receptor antagonists, including cimetidine (6.6 mg/kg IV q4-6h) or ranitidine (6.6 mg/kg IV q12h/q8h) should be considered for the treatment and/or prevention of gastric ulcers.

## THERAPEUTICS OF HYPERLIPIDEMIA AND HYPERLIPEMIA

Many horses—in particular miniature horses and donkeys, ponies, obese horses, and pregnant or lactating mares that are hospitalized for systemic disorders—are susceptible to

hyperlipidemia or hyperlipemia, a potentially fatal disorder of lipid metabolism. High-risk patients, especially those unable to eat or suffering inappetence, should be routinely monitored for glucose and triglyceride levels as well as serum hepatic enzyme alterations. If the patient has or develops hyperlipidemia, supplementation of IV fluids with dextrose (5% dextrose, 1-2 ml/kg/hr) and oral dextrose administration (corn syrup, 15-30 ml PO q8h to q6h) should be implemented.

The horses should be encouraged to eat if possible. If the triglyceride levels continue to elevate or the serum is grossly lipemic, additional intervention to lower plasma lipid levels is indicated. Options include insulin therapy (protamine zinc insulin, 30-40 IU per 200 kg subcutaneous [SQ]/IM q12h) in combination with oral or IV glucose supplementation with regular monitoring of glucose parameters. Alternatively, use of heparin (40-100 IU/kg SQ/IM q12h) has been reported to up-regulate lipoprotein lipase activity. Because of the potential of heparin to lower hematocrit and prolong clotting times, the hemat-

ocrit, prothrombin time (PT), and activated partial thromboplastin time (APTT) should be monitored regularly.

### Supplemental Readings

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## CHAPTER 1.7

# Preventing the Spread of Infectious Diseases

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Many of the clinical services associated with infectious diseases involve the diagnosis and treatment of individual animals with clinical disease or vaccination against a few infectious disease agents. The expectation is growing that veterinarians should also develop and oversee comprehensive programs to prevent the occurrence and transmission of infectious diseases and to protect animal herds from indigenous or exotic diseases. This chapter provides an overview of some of the fundamentals of epidemiology that can be applied in practice to prevent and control infectious diseases.

### DISRUPTING THE TRIADS OF INFECTION

Control and prevention of the transmission of infectious disease agents are addressed through alteration of one or more of the three elements of the triad of infection. This triad is the interaction among the host animal, the infectious disease agent, and the environment that manifests in infection, whether clinically or subclinically. The general objective is to minimize the probability that the host will become infected. For example, if the host's resistance is enhanced by vaccination, sound nutrition, and non-stressful environments and activities, the probability of in-

fection is reduced. Although such measures might not prevent infection in animals exposed to a very high dose of the agent, they may raise the infectious dose required for an animal to become infected.

Similarly, reducing the number or concentration of the infectious agents in the host's environment lowers the probability of infection. This reduction can be achieved through sanitation and use of disinfectants or other methods that inhibit or kill the agent or otherwise render the environment inhospitable for the agent. Alterations can be made to the environment to reduce directed exposure of the host to agents, such as by flies or other arthropod vectors. For example, insect screens, insecticides, and elimination of breeding environments might help reduce effective contact, survivability, and numbers of the vectors. General guidelines follow for the prevention of infectious disease transmission within the general context of the infection triad.

### HOST RESISTANCE

Prevention of disease transmission by promotion of host immunity and resistance depends on the route of infection, pathogenesis, and specific host barriers and immune

hyperlipidemia or hyperlipemia, a potentially fatal disorder of lipid metabolism. High-risk patients, especially those unable to eat or suffering inappetence, should be routinely monitored for glucose and triglyceride levels as well as serum hepatic enzyme alterations. If the patient has or develops hyperlipidemia, supplementation of IV fluids with dextrose (5% dextrose, 1-2 ml/kg/hr) and oral dextrose administration (corn syrup, 15-30 ml PO q8h to q6h) should be implemented.

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### HOST RESISTANCE

Prevention of disease transmission by promotion of host immunity and resistance depends on the route of infection, pathogenesis, and specific host barriers and immune

mechanisms that prevent infection by the specific agent under consideration. For example, prevention of leptospiral infection may depend on the presence of a viable skin barrier that has not been compromised by prolonged exposure to mud or water, as well as on specific circulating antileptospiral antibodies. Similarly, prevention of some viral or bacterial infections may depend on the degree of immunity offered through colostral antibodies or vaccination. Vaccination should be considered an adjunct to the prevention and control of infectious disease transmission and not a panacea. A key objective of vaccination is to promote herd immunity because few, if any, vaccines are 100% effective. Consequently, the overall efficacy of vaccination for an individual increases as the proportion of the herd vaccinated increases. Influenza vaccination of only 10 horses in a barn of 40, for example, would not provide as much protection to each of the 10 vaccinated horses as if all 40 were vaccinated.

## SANITATION

The goal of sanitation is to lower the concentration and number of infectious agents in the environment, thereby reducing the probability that an animal will become exposed to sufficient numbers of an infectious agent to become infected. Fastidious attention to sanitation of facilities, equipment, and personnel is a prerequisite for and the hallmark of successful infectious disease control programs. Personnel sanitation includes hand washing with disinfectant soap each time animals are handled and whenever the possibility of contamination with infectious material exists and the maintenance of clean work clothing and footwear. Personnel should use protective, disposable footwear, or footwear should be disinfected, depending on the objectives of the control program. Equipment used for multiple animals should be autoclaved or disinfected each time animals are contacted, and tools and heavy equipment used for feed or manure handling should be pressure-washed with appropriate sanitizing agents. Tools and equipment used for bedding or manure handling should not be used in feeding.

## FOMITES, RESERVOIRS, AND VECTORS

*Fomites* are objects that convey infectious agents from one animal to another. Examples include halters, lead ropes, shovels, pitchforks, thermometers, blankets, trailers, leg wraps, coveralls, and personnel clothing. Infectious agents also can be conveyed through vectors, which can be involved in the biologic transmission of an agent (in the case of some mosquitoes) or in mechanical transmission through simple movement or tracking of the agent from one location to another. Mechanical vectors can include any animal or object that could physically move an agent from one animal or animal location to another. Vectors can include ants, birds, mice, rats, cats, dogs, crickets, spiders, house flies, mosquitoes, cockroaches, personnel, thermometers, manure shovels, nasogastric tubes, or unsterilized needles. Some insects, such as cockroaches, can physically move infectious agents, such as salmonellae, from sewer drains to drinking water

and feed. Some fomites, such as thermometers, may behave as vectors of transmission if repeatedly conveyed from animal to animal.

A *reservoir* is an animal or other item (e.g., a cesspool) that supports multiplication and survival of an infectious agent and that is responsible (at least in part) for maintaining the infectious agent in the environment. Cats, birds, and mice may be reservoirs of some serotypes of salmonellae. Fecal shedding of the bacteria by these species can both amplify the amount of contamination and broadly disseminate the bacteria in the environment. Programs to prevent transmission of infectious diseases should minimize the potential for transmission associated with fomites, vectors, and reservoirs.

## MINIMIZING DIRECT AND INDIRECT CONTACT WITH OTHER ANIMALS

Transmission of infectious diseases is facilitated by management practices that permit direct physical contact among animals and indirect contact between animals and personnel, equipment, fomites, vectors, or facilities that have been contaminated with an infectious disease agent. Within a facility, animal movement should be restricted to prevent or minimize direct contact with other horses and to prevent indirect contact by exposure to excretions and secretions of other horses.

Indirect transmission occurs when infectious materials that may reside on such areas and items as the floor, bedding, stall doors, trailers, harnesses, tools, clothing, and boots are moved to areas with which susceptible animals have contact. Movement or transportation of animals suspected of shedding an infectious agent should follow routes that minimize exposure to other horses. Before other animals are permitted access to areas potentially contaminated during the movement of the animal, personnel should immediately clean and disinfect the exposed areas and equipment. Depending on the perceived need for stringent infectious disease control, personnel can minimize indirect contact by using separate equipment for each animal, including thermometers, harnesses, stall cleaning and feeding tools, and disposable booties or footwear used in a stall. Footbaths may be placed at strategic locations to reduce indirect contact through contaminated boots or horses' feet.

## ISOLATION AND QUARANTINE

Isolation facilities help to prevent transmission of an infectious agent within a herd or facility by providing a location away from the main population for animals possibly shedding an infectious disease agent. Such facilities should have restricted access and be physically removed from the main animal facilities, with separate feed, personnel, caretakers, equipment, and waste-removal procedures.

Quarantine is used to prevent new disease agents from entering a herd or facility. *Quarantine* is similar in concept to isolation in that a quarantine facility should be physically removed from the herd facilities, including any isolation facility, and should operate with feed, bedding, personnel, and equipment that do not have contact with any of the herd animals or facilities. Candidate animals are

quarantined for a period of time necessary to assess whether they have been exposed to or are shedding specified infectious disease agents. The quarantine period should exceed the maximum incubation or latent period for the specific agent and should be long enough to permit necessary diagnostic testing and interpretation of results before the animal is released into the herd.

## CLEANING AND DISINFECTION

Cleaning and disinfection involve frequent (usually daily) removal of infectious and potentially infectious material and killing of infectious agents after the burden of infectious or organic material has been removed from surfaces. Potentially infectious material can include soil, feed, manure, bedding, secretions, along with hair, tissue, and exudate. Cleaning usually involves several steps that progressively reduce or dilute the potential agent. After physically removing the material by scraping, digging, or high-pressure hosing, personnel should brush-scrub surfaces and floors (if not dirt) using a detergent with a surfactant that is compatible with the water hardness, water pH, and the disinfectant to be used. Several scrubblings and rinses may be required to remove the organic material (e.g., feces, bedding, and exudate).

After the organic material has been removed and the surface rinsed, an appropriate disinfectant for the specific agent(s) and facility should be applied. The cleaning process should avoid spreading material through dust or effluent into adjoining areas. Culturing surfaces to assess total bacteria counts after disinfection can be a means to evaluate the effectiveness of the cleaning and disinfection procedures.

## DISINFECTANTS

*Disinfectants* are chemicals that kill infectious disease agents or minimize multiplication and survival on soil, bedding, equipment, and facilities. The efficacy of disinfectants at a given dilution is generally based on their ability to reduce the concentration of a particular species of bacteria after a specified period of contact with the bacteria. Efficacy for most disinfectants diminishes as the organic contamination increases and increases as the contact time increases. Other factors that affect efficacy, depending on the disinfectant, include the type of anionic detergents used, ambient temperature, sunlight, water pH, and water hardness. The choice of disinfectant should consider the specific agent or agents being targeted, residual activity, degree of organic material, potential for contamination of feed and water, harmful side effects to animals and personnel, environmental contamination, and potential damage to equipment and facilities.

Most disinfectants fall into one of the following groups: alcohols, aldehydes, phenolics, chlorhexidine compounds, oxidizing agents, hypochlorite-type compounds, and quaternary ammonium compounds. Chlorhexidine compounds generally are not as effective against bacteria, viruses, and fungi as most other disinfectants, but they cause less tissue irritation. Phenolics are usually bactericidal and virucidal, especially for gram-positive bacteria and

enveloped viruses, but they do not kill spores. Phenolics can remain effective in the presence of some organic matter but may cause skin irritation and can become slippery after prolonged use on floors. Common oxidizing agents such as hydrogen peroxide are effective against anaerobic bacteria but not viruses, and they can cause corrosion of equipment. Recent products, however, have a broader range of efficacy, including enveloped and nonenveloped viruses, spores, and fungi. Alcohols are generally effective against gram-positive and gram-negative bacteria and enveloped viruses but not against spores or nonenveloped viruses. Alcohols are flammable, expensive, and can be irritating to eyes and tissues.

Quaternary ammonium compounds are effective against most gram-positive and gram-negative bacteria and enveloped viruses but not against nonenveloped viruses, fungi, or spores. Quaternary ammonium compounds can be inactivated by hard water and can be irritating. Hypochlorite disinfectants, such as common household bleach, are very effective against bacteria, fungi, algae, and both enveloped and nonenveloped viruses, but they are not effective against spores. The efficacy of hypochlorites is diminished by organic matter and sunlight, and they induce corrosion of metal surfaces. Aldehydes are effective in organic matter and have residual activity. They are broadly effective in killing viruses, bacteria, spores, fungi, and parasites. Formaldehydes, however, can be very toxic to animals and personnel. More specific information about disinfectants, including manufacturers, dilution, specific indications, and costs, is available from other reviews and on websites noted at the end of this chapter.

## SURVEILLANCE

*Surveillance* is a formal and ongoing assessment of the risk of an infectious disease agent in a herd or facility. Surveillance involves monitoring the presence or absence of an agent or the conditions that might favor an infectious agent. Examples may include routine culturing of feed, bedding, and drains for salmonellae, regular assessment of foal colostral antibodies to *Rhodococcus equi* to assess susceptibility of the foal population, or routine influenza serology to assess the status of vaccinal immunity and/or natural exposure. The aim of surveillance systems is to detect problems with infectious disease control program before the infectious disease agent is spread.

## FACILITIES DESIGN

One of the difficulties clinicians often experience in their efforts to control transmission of infectious agents is the animal facilities that are designed and organized in a way that is not compatible with many of the previously mentioned disease control strategies. Facilities should be designed and laid out to permit personnel to feed, clean, move, disinfect, quarantine, and isolate horses without exposing other horses. Careful consideration should be given to facility design and to construction materials to address the control and prevention of common endemic or indigenous infectious disease agents, such as salmonellae and influenza, as well as exotic disease agents.

## BIOSECURITY

*Biosecurity* encompasses the procedures and policies adopted to keep infectious disease agents out of a herd or population. Biosecurity involves measures that restrict access to the herd by animals or objects that are either infected or contaminated with an infectious agent. Infectious agents can gain entrance through pets, other horses, wildlife, visitors, equipment, or vehicles. Depending on the nature of the herd and of the specific agents being addressed by the biosecurity measures, personnel may need to shower and change before being permitted into the facility. Quarantine is a typical feature of most biosecurity programs, and animals reentering the herd or facility, as well as new animals, may need to be quarantined.

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# CHAPTER 1.8

## Nutraceuticals

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The term *nutraceutical* encompasses endogenous compounds that are supplied exogenously to facilitate normal functions and structures of the body. In the United States nutraceuticals for human use have been classified as dietary supplements since the passage of the Dietary Supplement Health and Education Act (DSHEA) in 1994, but compounds for use in animals are not covered by DSHEA. Because nutraceuticals are not classified as drugs, they cannot be administered parenterally and their manufacturers cannot claim that the compound treats or prevents disease. Another consequence of their unregulated status is that most nutraceuticals have not been rigorously tested for safety and efficacy. Because few guidelines regarding the acceptable ingredients and uses of nutraceuticals in veterinary medicine are available, the Association of American Feed Control Officials (AAFCO) has appointed a Nutraceutical Regulatory Advisory Panel to study these issues.

### SLOW-ACTING, DISEASE-MODIFYING OSTEOARTHRITIS AGENTS

Of the currently available nutraceuticals, slow-acting, disease-modifying osteoarthritis agents (SADMOAs) have been studied the most thoroughly. Even for these agents, however, insufficient data currently exist to allow definitive recommendations regarding their use in veterinary medicine. Orally administered SADMOAs include collagens, glycosaminoglycans (GAGs), chondroitin sulfate

(CS), glucosamine HCl, manganese ascorbate, green-lipped mussel (GLM, *Perna canaliculus*), methyl-sulfonyl-methane (MSM), and pentosan polysulfate (PPS). Numerous mixtures are used in human and veterinary medicine for both the prevention and treatment of arthropathies, and they have become increasingly visible in popular and scientific publications.

Most SADMOAs are involved in the synthesis of hyaline cartilage, which is composed of chondrocytes embedded in a nonvascular matrix of water, proteoglycans (PGs), and collagens. The PG macromolecule provides shock absorption to the cartilage matrix by attracting water from synovial fluid when the joint is at rest and releasing it during loading. PGs contain multiple GAGs that consist of CS and keratin sulfate and that are attached to a protein core that aggregates with hyaluronic acid. Manganese is a cofactor of proteoglycan synthesis, whereas ascorbate is involved in collagen formation. Glucosamine is an amino monosaccharide and a precursor of the GAGs of articular cartilage.

The main goal of chondroprotective therapy is to shift the net balance of chondrocyte metabolism from catabolic to anabolic processes because increased degradation and inadequate formation of cartilage components have been implicated in osteoarthritis (OA). *In vitro* studies of equine chondrocytes have found that exogenous glucosamine and CS stimulate the production of collagen and PG while inhibiting their degradation. SADMOAs may scavenge free radicals and may also exhibit noncyclooxygenase-mediated antiinflammatory effects.

## BIOSECURITY

*Biosecurity* encompasses the procedures and policies adopted to keep infectious disease agents out of a herd or population. Biosecurity involves measures that restrict access to the herd by animals or objects that are either infected or contaminated with an infectious agent. Infectious agents can gain entrance through pets, other horses, wildlife, visitors, equipment, or vehicles. Depending on the nature of the herd and of the specific agents being addressed by the biosecurity measures, personnel may need to shower and change before being permitted into the facility. Quarantine is a typical feature of most biosecurity programs, and animals reentering the herd or facility, as well as new animals, may need to be quarantined.

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# CHAPTER 1.8

## Nutraceuticals

LARA K. MAXWELL  
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A limitation of oral administration of SADMOAs is poor absorption of the intact molecules. PGs and CS are probably not absorbed intact from the gastrointestinal (GI) tract because large ionized macromolecules usually cannot cross the mucosa. However, fragments of the parent molecule have been found in synovial fluid and hyaline cartilage after oral administration of CS. Furthermore, glucosamine is a much smaller molecule than CS, and it is well-absorbed in rats, dogs, and humans after oral administration. Although most of the absorbed glucosamine is subject to immediate metabolism into simple sugars by the liver before entering systemic circulation, a tropism of the intact molecule for articular cartilage has been demonstrated.

Although glucosamine and CS have been widely studied, many of the human and veterinary studies have been plagued by inconsistencies and improper study design, which obscures the evaluation of supplementation. Although most efficacy studies in humans have found positive responses to oral therapy, conflicting results have been found. Symptoms of mild to moderate OA were alleviated with a combination of chondroprotective agents (e.g., glucosamine, CS, PPS), but there was little improvement in severe disease. Studies carried out in veterinary species have found beneficial effects of supplementation with GLM, PPS, or a mixture of CS, glucosamine, and manganese ascorbate. In horses, clinical signs of OA and navicular disease improved with administration of oral CS at 2.5 g once per day for 1 month or a mixture of glucosamine, CS, and manganese ascorbate (15:5:1) at 9 to 16.5 g twice per day for 1 to 2 months. Although it has been suggested that SADMOAs may be effective for the prevention of naturally occurring equine OA, this claim has not been studied.

Cautious optimism is presently warranted in the use of chondroprotective agents for the treatment of mild and moderate OA and navicular disease in horses, but their use requires time and patience. Rapid, dramatic improvement in the clinical signs of the disease is unlikely. Because these are slow-acting agents, 1 month of dosing may be required before signs of improvement are seen. If no improvement is seen by 2 months, clinicians might assume failure of response. In addition, clinicians must regularly assess horses to determine whether to continue supplementation or taper the dose after improvement is seen.

Although SADMOAs appear to be fairly safe, with a very low incidence of toxicity in laboratory animals and humans, a few areas of concern still exist. For example, although recommended by manufacturers for chronic supplementation, the safety of long-term use of these agents has not been determined in horses. Caution also may be indicated in the administration of chondroprotective agents to pregnant mares, as decreased birth rates have been reported in rats given high doses of CS. In addition, PPS supplementation in horses has been shown to mildly increase partial thromboplastin time. Because glucosamine and PPS are both heparinoids, they could have similar anticoagulant effects.

## PROBIOTICS

Directly fed microbials or *probiotics*, contain viable microorganisms that are administered orally to modulate the

GI flora, whereas *prebiotics* are substrates that select desirable microbes. Effective probiotic organisms are capable of GI colonization in both newborn and adult hosts, but their effects rarely persist, as they are unable to exclude preexisting bacteria. Probiotics may also stimulate a beneficial, nonspecific immune response.

Some probiotics are listed as feed additives in the AAFCO Official Publication in the United States. In addition, the European Commission's Scientific Committee on Animal Nutrition (SCAN) has found that most of these products intended for swine, poultry, and cattle are safe and effective. SCAN also deemed some probiotics unsafe, however, either because of the production of enterotoxins by *Bacillus cereus* and *Bacillus clausii* or because of the potential ability of some of the bacterial species to transfer antibiotic resistance. Although safety in horses has not been specifically addressed, multiple studies of several commercial probiotics in horses have reported no adverse effects.

Despite some conflicting results, a considerable body of evidence and several meta-analyses support the use of commercial probiotics in humans and farm animals. For example, they have been successfully used in humans to treat ulcerative colitis, bacterial vaginosis, and rotavirus or antibiotic-associated diarrhea. In food animals, bacterial probiotic therapy can decrease the incidence of diarrhea and act as a growth promoter. In cattle, live yeast cultures appear to increase the population of ruminal cellulolytic bacteria, dry matter intake, and milk production. Overall, however, these effects tend to be subtle, variable, and require selection of the appropriate microorganism for the condition and species being treated. Some of the variability in the response to probiotics may be a result of the host's health status; inoculation of the gut with beneficial bacteria should have little effect in animals with thriving GI flora.

As a result of the paucity of research and the equivocal results of bacterial supplementation in horses, little evidence exists of their beneficial effects. The most encouraging support for their use was increased growth in yearling foals supplemented with a mixture (Pronifer-MSB) of lactobacilli and a strain of *Pediococcus* bacteria. Unfortunately, SCAN decided that the strains of *Lactobacillus plantarum* and *Pediococcus acidilactici* used in this preparation might be capable of transferring tetracycline resistance to pathogenic bacteria. Studies of other bacterial probiotics in horses have been less promising. For example, several commercial preparations containing lactobacilli were ineffective in preventing salmonellosis or diarrhea in horses after colic surgery. These bacterial probiotics may be ineffective in horses because of their microbial species, which were apparently isolated from other host species. Because beneficial bacteria are highly species-specific, development of safe products derived from normal equine isolates, such as *Lactobacillus salivarius*, *Lactobacillus crispatus*, *Lactobacillus reuteri*, and *Lactobacillus agilis*, might effectively treat some conditions that can be ameliorated by bacterial probiotics in humans, such as antibiotic-associated diarrhea.

In contrast to the mixed results of bacterial probiotic supplementation in horses, yeast appears to be more effective and its results are consistent with its well-studied effects in cattle. Administration of live yeast cultures

(Yea-Sace<sup>1026</sup>), *Saccharomyces cerevisiae*, to pregnant and lactating mares at 20 g/day improved feed digestibility and milk production. When given to yearling foals at 8 g/day and to 10-week-old foals at 10 g/day, this product also increased feed digestibility and growth rate. These effects persisted for 1 to 9 weeks after supplementation. The European Union has approved the use of this strain of *S. cerevisiae* in cattle after SCAN's recommendation. Yeast supplementation with this product can be considered in underweight foals and adult horses to facilitate weight gain and might also assist mares with insufficient milk production.

## NUTRITIONAL ERGOGENIC AIDS

*Ergogenic nutraceuticals* are naturally occurring compounds that enhance work output through increased aerobic or anaerobic capacity. Numerous advertisements claim that specific substances are strongly ergogenic and will greatly increase speed, endurance, or muscle mass in horses. Ergogenic products for humans and horses have existed for years but until recently have failed to demonstrate a significant benefit in controlled studies. Increased interest in this area has followed recent findings that  $\beta$ -hydroxy  $\beta$ -methylbutyrate and creatinine may truly be ergogenic in humans. Unfortunately, preliminary studies in humans and animals are often subject to methodological errors or are published as abstracts, obscuring the interpretation of efficacy. Although several of these compounds appear to enhance performance in humans, their use in horses has not been established.

### $\beta$ -Hydroxy $\beta$ -Methylbutyrate

$\beta$ -Hydroxy  $\beta$ -methylbutyrate (HMB) is a metabolite of leucine, an essential amino acid. Because leucine increases protein synthesis and inhibits its degradation in striated muscle *in vitro*, advocates of HMB supplementation suggest that it increases muscle mass in athletes. Although HMB does increase feed efficiencies and growth rates of underfed farm animals, other experiments have failed to confirm that HMB affects protein turnover or uptake by skeletal muscle. Preliminary evidence in horses suggests that HMB administration may lower plasma triglycerides, increase plasma lactate, and decrease heart rate.

If horses respond to HMB similarly to humans, supplementation could help condition unfit horses; several studies indicate that HMB increases the lean body mass of untrained humans with initiation of exercise. Supplementation of fit horses may be ineffective, however, because HMB administration in trained humans does not have beneficial effects. Despite promising studies in humans, the ergogenic efficacy of HMB in unfit horses requires further study before it can be recommended during early training.

### Carnitine

The liver uses lysine and methionine to synthesize L-carnitine, which is involved in fatty acid oxidation. Because some carnitine is absorbed in horses after oral administration and carnitine levels in equine muscles increase with training, supplementation will purportedly enhance the capacity for oxidative endurance exercise in horses. This

upsurge in muscular carnitine concentration probably results from an exercise-induced rise in the mitochondrial density, however, rather than from the accumulation of free carnitine. In addition, several studies have demonstrated that carnitine supplementation does not promote fatty acid oxidation or exercise tolerance in humans. Therefore at this time no evidence supports the use of carnitine in horses as an ergogenic aid.

### Chromium

Chromium (Cr) is an essential trace mineral that potentiates the action of insulin on carbohydrate metabolism. On the basis of this effect, humans have oversupplemented with Cr in an attempt to increase their energy during high-intensity exercise by enhancing the uptake of glucose by muscle cells. Although Cr supplementation has been shown to increase the rate of glucose clearance from the plasma of horses, it has provided no other apparent benefit in yearling horses and has not enhanced high-intensity performance in humans. In contrast, increased lean body mass has been reported in humans and food animals after Cr administration. Beneficial effects of administration may be the result of the amelioration of a preexisting Cr deficiency that has been described in humans, however. Although the need for supplementation in horses is unclear because nutritional requirements have not been established, no adverse effects were noted when yearling horses were given 105 to 420 g/kg of total diet for 112 days.

### Creatine

Creatine is integral to the regeneration of adenosine triphosphate (ATP) from adenosine diphosphate (ADP). Because the cleavage of available ATP composes the fastest part of the anaerobic system, enhancement of regeneration could increase power during anaerobic activity. Creatine supplementation in humans does appear to be ergogenic because muscle creatine stores increase with oral supplementation and the ability to perform brief, high-intensity exercise, such as weight lifting, is enhanced. In contrast, endurance exercise is unaffected or worsened by supplementation. No studies of the ergogenic effects of creatine in horses have been performed, but if they respond similarly to humans, creatine supplementation may not be beneficial because most equine sports require some aerobic component. Orally administered creatine also appears to be poorly absorbed in horses. Furthermore, because the safety of long-term creatine supplementation in humans is questionable, chronic supplementation could be problematic in horses.

### Coenzyme Q10

Coenzyme Q10, or *ubiquinone*, is a component of the electron transport system of mitochondria and an antioxidant with immunostimulatory properties. Limited studies carried out in humans suggest that coenzyme Q10 may be beneficial in a number of disease conditions, including cancer, acquired immunodeficiency syndrome (AIDS), and cardiomyopathy. However, administration of coenzyme

Q10 in humans and dogs with congestive heart failure failed to improve cardiac function. In addition to the use of coenzyme Q10 for the treatment of disease, several manufacturers of human and equine products have stated that coenzyme Q10 enhances endurance during exercise, but little evidence exists to support this claim. For example, human studies provide conflicting results of ergogenic benefits, and equine studies have not been published. Coenzyme Q10 does not presently have a recognized place in equine medicine.

### Plant Sterols— $\gamma$ -Oryzanol

$\gamma$ -Oryzanol is a plant sterol that is found in rice bran. Some advertisements claim that because of its sterol structure, this compound has anabolic properties and will increase muscle mass and power output in human and equine athletes. Published studies in humans do not support this claim, however, and only anecdotal reports are currently available in horses. In fact, evidence exists that  $\gamma$ -oryzanol has catabolic effects and disrupts endocrine function in laboratory animals. Although currently no ev-

idence exists to support the use of this supplement in horses, ongoing research in humans and laboratory animals indicates that the antioxidant properties of  $\gamma$ -oryzanol may be useful in the treatment of some types of cancer, cardiac disease, and hypercholesterolemia.

### Supplemental Readings

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## CHAPTER 1.9

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# Pharmaceutical Compounding

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SARAH SELLERS

*Barrington, Illinois*

CYNTHIA KOLLIAS-BAKER

*Gainesville, Florida*

In an ideal world, dosage forms would exist to treat all conditions in all animals. In reality, however, this goal is impossible. Manufacturers are unable to anticipate every current and future need, and they are often restricted by drug development costs and the lengthy process of Food and Drug Administration (FDA) approval for various products. To address this problem, veterinarians and pharmacists within certain limitations are allowed to compound pharmaceutical preparations.

### DEFINITIONS

*Secundum artem—according to the art*

In general terms, *compounding* can be defined as the art and science of mixing ingredients, which may be active, inactive, or both, to create a specific dosage form to meet an individual patient's needs. In equine medicine, compounding may be necessary to treat a neonatal foal with a unique formulation of electrolytes and amino acids or an adult horse suffering from equine protozoal myelo-

encephalitis (EPM) with a single oral formulation containing pyrimethamine and sulfadiazine.

Compounding, however, is not without risk; certain compounded dosage forms have caused injury and death in both animal and human populations. An example is the recent death of cattle caused by the presence of endotoxins in a parenteral product prepared from spectinomycin that was only approved for oral use. Clinicians therefore must use science-based evidence and a risk-versus-benefit analysis when making decisions concerning the use of compounded drug products in their patients.

Pharmacies that specialize in veterinary compounding have been growing in number and reaching large consumer bases through the Internet. Many sites offer anecdotal treatments and compounded therapies that fall outside the scope of the valid veterinarian/patient/owner relationships that are required for legal compounding. Currently the FDA is using broad discretion in the regulation of these pharmacies, but veterinarians should be aware that legal ramifications exist for the use of compounded products.

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Pharmacies that specialize in veterinary compounding have been growing in number and reaching large consumer bases through the Internet. Many sites offer anecdotal treatments and compounded therapies that fall outside the scope of the valid veterinarian/patient/owner relationships that are required for legal compounding. Currently the FDA is using broad discretion in the regulation of these pharmacies, but veterinarians should be aware that legal ramifications exist for the use of compounded products.

## UNDERSTANDING RISK

*Above all else, do no harm.*

The use of compounded drugs presents unique risks to patients. When using compounded dosage forms the veterinarian and pharmacist are entirely accountable for the safety and efficacy of the product, and it is essential that they thoroughly understand this responsibility and the associated risks. Above and beyond the associated pharmacologic effects, compounded products may present higher risks for adverse drug events and/or therapeutic failures than FDA-approved medications. For example, although manufacturers of FDA-approved medications must adhere to strict quality control practices (Good Manufacturing Practices) during all phases of drug manufacturing, no such requirements exist for compounding pharmacies. As a result, analyses of compounded drug products often reveal that the actual drug concentrations vary tremendously from the labeled amounts. Some compounded antimicrobial products have also failed microbial assays, suggesting poor efficacy.

In addition, during the drug-approval process the product sponsor must demonstrate that products intended for nonintravenous administration have adequate and predictable bioavailability to ensure efficacy and safety. Again, compounders are under no such obligation. Therefore compared with an FDA-approved drug, a compounded product may vary significantly in the rate and extent of drug release from dosage forms, which may affect both the pharmacokinetic and pharmacodynamic properties of the drug. These changes may confound the clinician's ability to predict responses to treatment and could cause direct injury or delay effective therapy. Although careful adherence to good compounding practices can minimize these effects, other factors, including particle size and crystalline states of chemicals, may contribute to overall absorption characteristics. For example, when the contents of a capsule are dissolved or suspended in an aqueous environment or when a chemical is applied in a topical gel, the resulting dosage form may not always have the same absorption properties as the original product.

The greatest risk of compounded products may be associated with compounding from bulk active chemicals, in which case the quality and purity of the starting materials cannot be ascertained. Currently bulk active chemicals can be purchased through brokers, over the Internet, or through pharmaceutical repackagers, making a trace on the history of the drug difficult. For example, in 1998 congressional hearings cited compounding pharmacies as one of the primary routes for the entry of counterfeit drugs into the United States. In addition, in the U.S. pharmaceutical industry, bulk chemicals are extensively tested for purity and potency before they are manufactured into a dosage form.

Recent FDA inspections of bulk suppliers to pharmacies, however, have resulted in warning letters citing numerous quality-related violations, including suspect expiration dates, lack of control for antibiotic cross-contamination, and substitution of industrial-grade chemicals for U.S. Pharmacopeia (USP) or pharmaceutical grade. Of particular concern are drug products intended to be sterile, nonpyrogenic dosage forms. For instance, one FDA inspection of a pharmaceutical repackager revealed that raw industrial-

grade dimethyl sulfoxide (DMSO) was repackaged as pharmaceutical-grade (USP). If this DMSO had been used to compound an injectable dosage form, as is commonly done to treat central nervous system (CNS) inflammation, complications from contaminants or pyrogens could result in injury or death.

## BENEFITS

*Meeting the patient's need*

Despite the risks associated with compounded products, clinical situations may exist in which their use is necessary and appropriate. For example, until quite recently the use of the potentiated sulfonamide combination, pyrimethamine and sulfadiazine, was the most commonly recommended treatment for EPM. Because no human or animal FDA-approved product exists that contains both compounds at the required doses, products compounded from approved oral formulations of each individual drug were created.

## REGULATION

*Protecting health and safety*

In general, a veterinarian appropriately may compound or request a pharmacist to compound a product to treat an individual patient if the following conditions are met:

1. A legitimate medical need exists in which the health of an animal is threatened and suffering or death would result from failure to treat the affected animals.
2. A need exists for an appropriate dosage regimen for the age, size, species, or medical condition of the patient, but no approved animal drug exists that can be used as labeled or in an "extra-label" manner.
3. No human-label drug is available in the necessary dosage form.
4. Some other rare extenuating circumstance exists. For example, the approved drug cannot be obtained in time to successfully treat the animal.

After the previous determinations are made, the following criteria should be met and precautions observed:

1. The product must be dispensed by a licensed veterinarian or a licensed pharmacist in receipt of a valid prescription by a veterinarian. Dispensing should be within the confines of a valid veterinarian/client/patient relationship.
2. The veterinarian must ensure all the following:
  - a. The safety and efficacy of the compounded new animal drug are consistent with current standards of pharmaceutical and pharmacologic practices. For example, known incompatibilities should be avoided.
  - b. Appropriate steps must be taken to minimize the risk of personnel exposure to potentially harmful ingredients in the preparation process.
  - c. Procedures must be instituted to ensure that appropriate patient records for the treated animals are maintained.

3. All drugs dispensed to the animal owner by the veterinarian or a pharmacist must bear labeling information, which is adequate to ensure proper use of the product. This information should include the name and address of the veterinary practitioner; the active ingredient(s); the date dispensed (with an expiration date); directions for use specified by the practitioner; the class/species or identification of the animals; the dosage, frequency, route of administration, and duration of therapy; and any cautionary statements. Veterinarians who compound or prescribe compounded medications according to these guidelines would be considered to be engaged in extemporaneous compounding and would not ordinarily be subject to regulatory action.

## FOOD AND DRUG ADMINISTRATION CENTER FOR VETERINARY MEDICINE

The FDA's Center for Veterinary Medicine (CVM) allows for the compounding of animal drugs under the 1994 Animal Medicinal Drug Use Clarification Act (AMDUCA). This statute expanded the veterinarian's authority to use drugs in an off-label manner, including the right to compound with use of FDA-approved dosage forms. AMDUCA does not allow for the compounding of drugs from bulk active substances, and any products resulting from such substances are considered new animal drugs and are subject to the FDA drug-approval process.

The FDA Modernization Act of 1997 allows for the compounding of human drugs from bulk chemicals if the bulk substance is an ingredient of a currently approved product, is covered under a current USP monograph, or appears on an FDA list of drugs that can be compounded but does not appear on a list of bulk substances withdrawn from the market for safety reasons. Human compounding regulations are in sharp contrast to current animal compounding regulations. These regulations become an important consideration for the veterinarian who outsources compounding to a pharmacy that may compound exclusively from bulk active chemicals.

## PROFESSIONAL GUIDANCE

### American Veterinary Medical Association

The position statement by the American Veterinary Medical Association (AVMA) on compounding was adopted in January of 2001 and developed in part over concerns with the growing number of veterinary compounding pharmacies. The AVMA position states that the decision to use a compounded drug should be established by veterinarians, not pharmacists. Furthermore, according to the AVMA, the use of a compounded drug should be restricted to the following:

1. Drugs for which safety and efficacy have been demonstrated for the compounded form in the target species
2. Disease conditions for which response to therapy or drug concentration can be monitored
3. Those individual patients for which no other method or route of drug delivery is practical

The AVMA position also states that use of compounded drugs should not be based on ease of administration.

### American Association of Equine Practitioners

The position of the American Association of Equine Practitioners (AAEP) on compounding highlights the need for valid client/patient/veterinarian relationships and notes that horse-side compounding by veterinarians may be necessary to best meet the individual needs of some patients. The AAEP does not, however, support manufacturing under the guise of compounding, especially when preparations are being produced en masse and sold over the counter. In addition, the association recognizes that some veterinary pharmacies may encourage the use of illegally manufactured drugs or drugs purported to be effective only on the basis of anecdotal evidence.

## PRACTICAL CONSIDERATIONS

### Compounding Pharmacies—Points of Discussion

When a veterinarian recognizes a need for a compounded product and chooses to have a pharmacy compound that product, numerous issues must be discussed with the pharmacist. How will the drug be prepared? What are the starting materials? Will bulk chemicals be used? If the answer to the last question is yes, then the pharmacist is in violation of AMDUCA and the AVMA position statement on compounding, in which case the veterinarian assumes substantial risk in using this product. Will the end product be analyzed for accurate drug concentrations and assessed for microbial and endotoxin contamination? Finally, is the dosage form demonstrably difficult to compound (e.g., a sterile dosage form when only nonsterile ingredients are available)?

The veterinarian should ask such questions to aid in his or her own decision-making process and to ensure the safety and efficacy of the compounded dosage forms used in specific patients. These questions can also provide important information that may help explain potential causes for unexpected therapeutic outcomes.

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## CHAPTER 1.10

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# Drug Testing in Performance Horses

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Equestrians, veterinarians, and the horse-loving public are becoming increasingly concerned about the use of drugs and medications in horses participating in athletic competitions. Although therapeutic medications are beneficial, their overuse and the administration of illegal drugs can mask serious injuries and alter performance. Therefore private and government regulatory officials have been assigned to develop drug and medication rules to protect the health and welfare of the horses and equestrians, ensure a fair and level playing field for all competitors, and safeguard the public interest when parimutuel wagering is involved.

### TEST SAMPLES

In the majority of programs, urine is the sample chosen for testing because it is easy to obtain and because most drugs or their metabolites tend to be present in relatively high concentrations in urine. Urine samples are usually collected from horses after competitive events. In racehorses, sample collection is usually a straightforward procedure. After the race the winner and one or two other horses (usually chosen at random) are taken to a secure and isolated detention barn, where they are bathed, cooled down, and allowed access to water. Most horses urinate sometime during this cool-down period. In contrast, collecting urine in show horses is often problematic. Many show horses compete throughout the day, and they often appear shy, refusing to urinate in the presence of the technicians.

Blood samples are also commonly collected, but they are primarily used to control the use of authorized medications, such as nonsteroidal antiinflammatory drugs (NSAIDs). Threshold concentrations for these agents are set in serum or plasma, and the laboratories analyze the collected samples to ensure that the maximum allowed concentration for the authorized medication is not exceeded.

In general, the drug-testing methods used by laboratories today are not sensitive enough to test for unauthorized substances in serum or plasma. For example, low doses of some medications, such as detomidine, mepivacaine, and acepromazine, although pharmacologically active, are not detectable in the plasma or serum. In contrast, many therapeutic medications can be detected in the urine for days and even weeks after they were last administered and long after they cease to have any signifi-

cant pharmacologic activity. For this reason a few states, such as California, have adopted "decision levels" or "thresholds" for a limited number of therapeutic drugs on the basis of urinary concentrations. The philosophy is to prevent horses from competing under the influence of unauthorized medications while still allowing veterinarians to provide the best quality medical care possible.

### SAMPLING

Procedures for sample collection must take into consideration both scientific and legal aspects. The drug-testing process begins when a sample of urine and/or blood is collected. The collection container must be new, clean, and sealed, and the sample must be obtained in a manner that prevents possible contamination from the environment. The sample then is sealed with tamper-proof tape and secured for transport to the laboratory. Accurate records of sample collections and shipments must be maintained to establish an appropriate chain of custody. The laboratories must also keep accurate records as to when the samples are received and document the internal chain of custody. In addition, security procedures must be in place to prevent the samples from being tampered with or compromised in some other manner.

### DRUG-TESTING METHODOLOGY

#### Sample Screening

Once at the laboratory the sample is subjected to one or more screening tests. Ideally, screening methods are rapid and sensitive, but they may not be highly specific. In the United States the three most common screening methods used to detect the presence of drugs in equine urine samples are thin-layer chromatography (TLC), enzyme-linked immunosorbent assays (ELISAs), and instrumental analysis.

#### *Thin-Layer Chromatography*

Racing laboratories have used screening methods based on TLC for 40 years. TLC procedures are time-consuming, labor-intensive, and highly dependent on technologist interpretation. The sensitivity of drug detection for TLC is inferior to modern methods of chromatography. In general, most compounds of interest can be detected with TLC only if their concentration is above 100 ng/ml. TLC

has retained favor as an analytic method, however, because of its simplicity, dependability, low cost, and capacity to simultaneously detect a wide range of substances in a single analysis.

During TLC analysis, portions of the test sample undergo a series of chemical extractions designed to separate any drugs from endogenous substances and concentrate them in a small amount of solvent. The extracts are then applied, "spotted" on to thin glass plate, which is coated with an adsorbent material such as silica gel. The plate then is placed into a tank with a small volume of solvent (mobile phase). Drugs and other compounds are carried up the plate by capillary action by the mobile phase at a rate and distance that depends on their physiochemical properties. Different drugs may have similar migration patterns; therefore the identification of a drug based on TLC analysis is only tentative. TLC has not been used as a confirmatory technique for more than 20 years. A confirmatory method using mass spectrometry must be conducted on any sample with a tentative TLC finding.

#### **Enzyme-Linked Immunosorbent Assay**

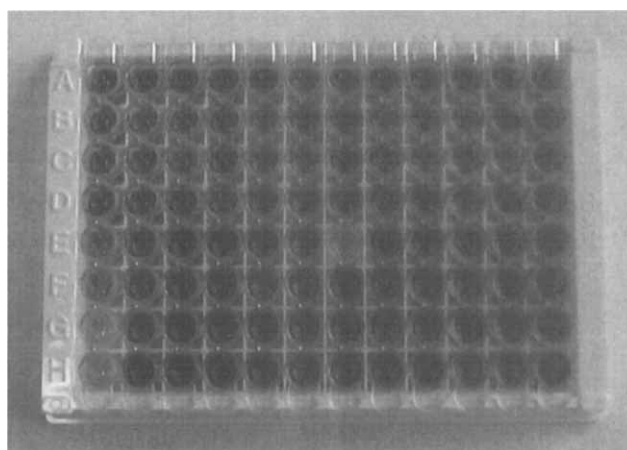
ELISA has become a very common method in routine equine drug testing because of its simplicity and sensitivity. The majority of laboratories in the United States use ELISA to complement their TLC testing methods, although several laboratories have recently developed testing schemes based solely on ELISA tests. The principal components in enzyme immunoassays are a drug labeled with a specific enzyme, an antibody specific to the drug, and a substrate capable of producing a measured optical signal (color change) when initiated by the enzyme and the test sample. The antibodies used in ELISA tests are specific for one drug or a drug class in which members have a similar chemical structure.

In the test the enzyme-labeled drug binds to the antibody, which results in a color change when the substrate is added. If drug is present in the test sample, it competes with the enzyme-labeled drug for binding sites on the antibody. Because less of the enzyme-labeled drug is bound to the antibodies, little or no color change occurs when the substrate is added (Figure 1.10-1). The testing process is automated, with microtiter plate readers that rapidly screen the plates at their optimal wavelengths and calculate the test results with vendor-supplied software. When appropriate standards and calibration samples are used, ELISA can provide semiquantitative results.

The principal advantage of ELISA tests is their extreme sensitivity. Limits of detection of 1 ng/ml are possible for many substances. As with any antibody-based test, non-specific cross-reactions can occur. Therefore, as with TLC, ELISA results represent only tentative drug identifications. A more specific test must be used to confirm the presence and the identity of the drug.

#### **Instrumental Analysis**

With the availability of lower-cost instruments and automated sample preparations, instrumentally based drug-testing programs with the use of gas chromatography/mass spectrometry (GC/MS) and liquid chromatography/mass spectrometry (LC/MS) are rapidly becoming the gold standard for equine drug testing. These instrumental



**Figure 1.10-1** A developed ELISA plate with a suspect sample depicted on row E, column 7. The 96-well plate configuration allows the analysis of 88 samples and 8 controls (shown at the left).

approaches provide a wide range of coverage (>500 drugs) and excellent sensitivity and specificity. Limits of detection less than 1 ng/ml are possible if conditions for extraction and chromatographic separation are optimized.

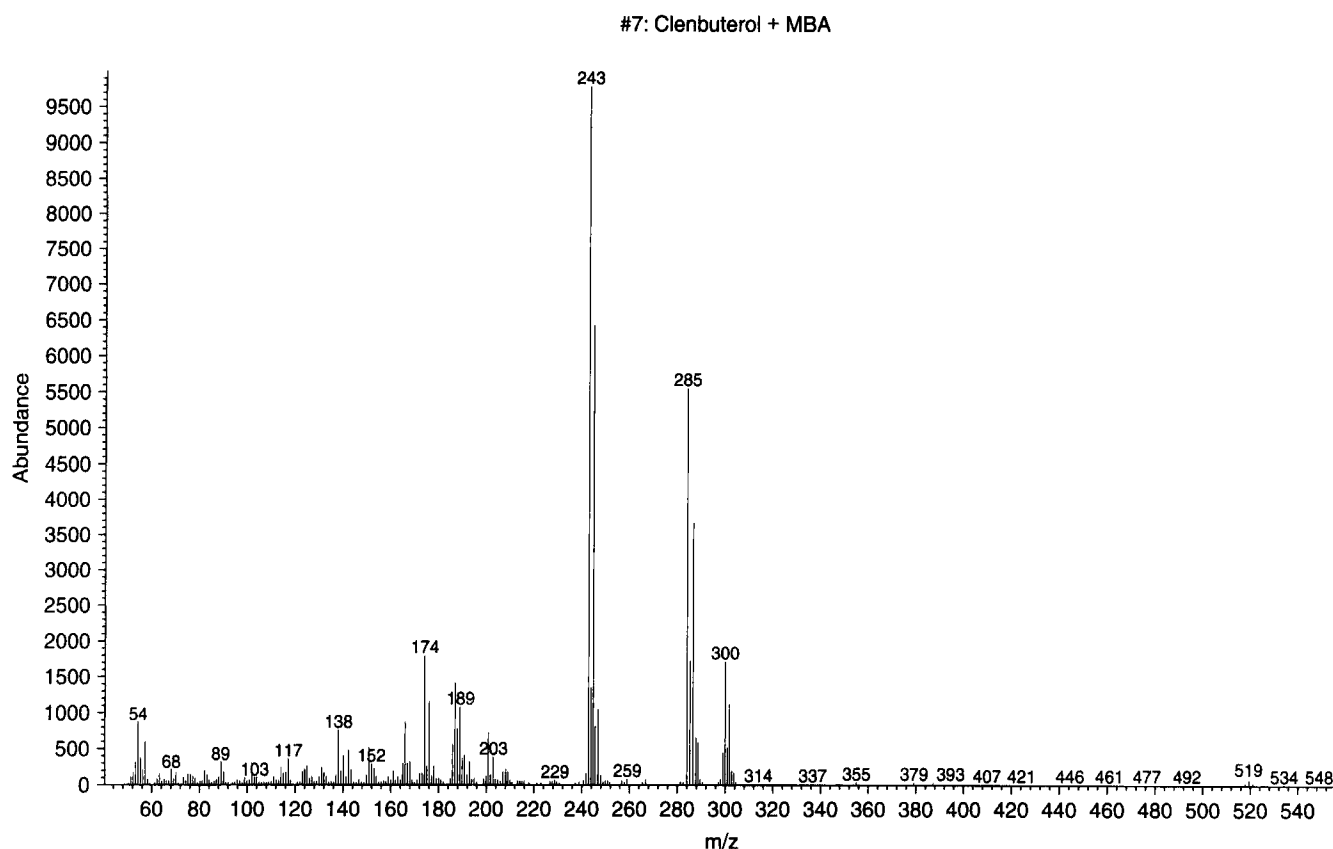
MS works through the strategy of "divide and conquer" by breaking down the chemical structure of the molecules into smaller, more easily identifiable pieces. The smaller fragment ions, as well as the original ionized parent molecules, are focused into an analyzer, where the mass-to-charge ratio and the abundance of each ion are measured. A plot of the abundance of the ions versus their mass/charge ratios is referred to as the compound's *mass spectrum* (Figure 1.10-2). In the past gas chromatographs (GC) have primarily been used to separate compounds of interest in a sample before analysis is performed on a mass spectrometer (GC/MS). Recently, however, the use of high-performance liquid chromatographs as separation instruments has increased. LC instruments permit the identification of many drugs that are not amenable to gas chromatography because they are too polar, are not volatile, or have very high molecular weights.

Sample screening with GC/MS and LC/MS procedures consists of small urine volumes separated by mixed-mode, solid-phase extraction into two fractions—an acid/neutral and a base—followed by direct analysis. A modified GC/MS system configured for large-volume injection (~40-50  $\mu$ l) has proven to be a sensitive, high-throughput, precise, and rugged system that has clear advantages for drug screening of the basic drug fraction. The LC/MS ion trap with an inline photo-diode array detector has been used for the combined acid/neutral fraction because this fraction by and large contains compounds that are not volatile or are otherwise unsuitable for GC/MS.

#### **Confirmatory Analysis**

If the results of a screening test indicate that the sample may contain a nonpermissible drug or medication, laboratory personnel perform more rigorous testing on the sample to confirm the presence of the suspected drug or medication. This confirmatory testing is carried out on





**Figure 1.10-2** Mass spectrum of Clenbuterol-MBA derivative as determined by GC/MS analysis.

samples with positive screening test results, regardless of whether the testing method used was TLC, ELISA, or instrumental analysis. To protect the integrity of the drug-testing program and to enable the analytic findings to withstand legal challenge, the results of the confirmatory testing process must be indisputable. To that end the use of mass spectral analysis with either LC/MS or GC/MS methods has become the industry standard for confirmatory testing. The mass spectrum of each drug is unique, and therefore the use of mass spectral data for confirmatory analysis provides a very high degree of specificity. Regardless of which separation instrument is used, the mass spectral results generated by GC/MS and LC/MS provide a unique drug “fingerprint” that is conclusive evidence for the presence of the drug.

### SPLIT SAMPLE ANALYSIS

As described previously, before a reputable laboratory reports that a sample is positive for a drug or medication, the sample undergoes a rigorous screening and confirmatory testing process with the use of validated analytic procedures. Nevertheless, a split, or referee, sample analysis is permitted in most racing jurisdictions. The referee or split sample consists of a small amount of the original sample, which is poured into a separate container (“split off”) immediately after collection. The referee sample is stored frozen at a secure site, physically separate from the pri-

mary testing laboratory. If the primary laboratory reports that a sample is positive for an unauthorized substance, the owner or trainer of the horse implicated has the option to have the referee sample sent to a second independent laboratory. This laboratory repeats the analysis to confirm the presence of the unauthorized substance. If the second laboratory fails to confirm the positive finding of the primary laboratory, no regulatory action is taken against the trainer or owner.

### AUTHORIZED MEDICATIONS

The use of NSAIDs in horses is extremely common. Racing regulations in most U.S. jurisdictions permit one NSAID to be present in postrace serum samples but limit the maximum concentration of the drug permitted in that sample. For example, in most jurisdictions phenylbutazone is limited to a maximum concentration of 5.0  $\mu\text{g/ml}$  of serum. Quantification of NSAIDs in postrace serum samples is routinely performed with HPLC through the use of either ultraviolet or MS detection.

### SUMMARY

Drug-testing programs are implemented to enforce drug and medication rules. Most programs consist of a two-part testing process that uses urine as the primary sample type. All samples are tested in the preliminary screening

process, and any samples with suspicious results undergo an additional round of confirmatory testing.

The most common drug violations in equine drug testing programs are overages of authorized medications. Veterinarians must remain aware of the drug and medication rules under which their clients compete and follow recommended withdrawal guidelines to avoid unintended positive urine samples.

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# SECTION II

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## Infectious Diseases

*Edited by Dr. Steeve Giguère*

### CHAPTER 2.1

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## Equine Viral Arteritis

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**E**quine viral arteritis (EVA) is a worldwide infectious disease that is characterized by panvasculitis that induces edema, hemorrhage, and abortion in pregnant mares. EVA can be confused with other equine diseases and needs to be considered in sporadic and epizootic respiratory syndromes, foal death associated with respiratory and/or enteric signs, or sudden death in foals. Velogenic isolates of equine arteritis virus (EAV) can induce severe and fatal disease in adults. Seropositivity can vary by breed, and the majority of the Standardbred horses in the United States are seropositive. Recent outbreaks or epidemics resulting in neonatal death in the United States have been associated with carrier warmblood sires or semen used to breed seronegative warmblood mares. Natural outbreaks of EVA, characterized by transient clinical signs and abortion in pregnant mares, contrast to experimentally induced disease, which features high mortality and prominent systemic vascular necrosis. Blood vessel cells are the major—but not exclusive—targets of the EAV. Lung, intestine, kidney, the reproductive tract, and occasionally the placenta are important viral replication sites that favor the spread of the virus.

EAV is an enveloped, spheric, positive-stranded RNA virus with a diameter of 50 to 70 nm. EAV is a nonarthropod-borne virus that is classified as a member of the new order *Nidovirales*, which also includes the bigeneric family *Coronaviridae* within the family *Arteriviridae* with porcine respiratory and reproductive syndrome virus, simian hemorrhagic fever virus, and lactate dehydrogenase-elevating virus. EAV is genetically similar to coronaviruses but has a dissimilar viral structure and a complement-fixing antigen—but no hemagglutinins. Genetic diversity is recognized among field isolates.

### CLINICAL SIGNS AND CARRIER STATE

The EAV isolates differ in virulence and consequently induce clinical signs and lesions of varying severity. Clinical signs may be absent or include pyrexia up to 41°C that

develops after an incubation period of 3 to 14 days (6 to 8 days after genital exposure) and that can endure for 2 to 9 days. Depression, anorexia, leukopenia, limb edema, stiffness of gait, rhinorrhea and epiphora, conjunctivitis, and rhinitis can be observed. Edema of the periorbital and supraorbital areas, midventral regions, scrotum, prepuce, and mammary gland; urticarial rash; and abortion also occur. Less frequently, severe respiratory distress, ataxia, mucosal papular eruptions, submaxillary lymphadenopathy, and intermandibular and shoulder edema may be observed. EAV can be associated with epidemic abortion and is occasionally fatal in adults but more often can be fatal for foals. When neonates are not protected by passive maternal immunity, they may present with sudden death or severe respiratory distress followed by death.

Affected intact males may become long-term carriers and shed EAV in the semen; sires that shed EAV in their semen serve as a reservoir for the virus within the equine population. This continuous viral replication occurs within the epithelium of the stallion's accessory glands. Infected sires and semen have resulted in restrictions for the international movement of horses and semen. Mares infected with EAV as a result of being bred to a shedding stallion do not appear to experience fertility problems. After experimental infection, stallions presented temporary subfertility, reduced libido, and decreased sperm motility for up to 6 to 7 weeks. No long-term effects on semen quality have been observed in naturally infected stallions.

Clinical pathologic findings in affected foals include hypoxia, hypercapnia, respiratory acidosis sometimes complicated by metabolic acidosis, neutropenia/neutrophilia, lymphopenia/lymphocytosis, thrombocytopenia, and hyperfibrinogenemia. However, abnormal values may be inconsistently present, are highly variable, and are not diagnostic for EVA. Arterial blood gas values in affected foals diagnose severe disease of the respiratory system, but these abnormalities may be seen in a variety of neonatal diseases of horses—including bacterial sepsis,

acute respiratory distress syndrome, congenital cardiac anomalies, and other viral diseases, such as equine herpesvirus 1 infection. Experimentally infected mature horses consistently present with biphasic leukopenia, neutropenia, and lymphopenia after infection.

## **PATHOLOGY AND PATHOGENESIS**

Gross lesions are the expression of the vascular pathologic changes: edema; congestion; and hemorrhage of the subcutaneous tissues, lymph nodes, viscera and, especially in foals, the lungs. Histologically, pulmonary and systemic panvasculitis, bronchointerstitial pneumonia, lymphoid tissue necrosis, renal tubular necrosis and interstitial nephritis, and ulcerative dermatitis with vasculitis can be observed. Necrotizing vasculitis that involves the testes, epididymis, vas deferens, ampullae, prostate glands, and vesicular and bulbourethral glands has been described. Fetuses and fetal membranes are often expelled without premonitory signs of abortion and can be autolyzed or well-preserved. Lesions in the fetus are rare.

EAV has a characteristic pathway of infection, as follows:

1. Respiratory epithelium and alveolar macrophages (24 hours postinfection [PI])
2. Satellite lymph nodes, especially bronchial lymph nodes (48 hours PI)
3. Bronchopulmonary lymph nodes, endothelium, and circulating monocytes (3 days PI)
4. Systemic distribution with localization within macrophages and dendritic cells of lymphoid tissue
5. Endothelium and medial myocytes of blood vessels and mesothelium (6-8 days PI)
6. Most severe damage to blood vessels (10 days PI)
7. Decrease of EAV in all the locations except the tunica media of small muscular arteries (>10 days PI)
8. Renal tubular epithelium (EAV persisting for additional 2 weeks)

Infective EAV is no longer detectable in most tissues after day 28 after experimental infection, with the exception of the reproductive tract of some colts and stallions. Abortion is associated with and caused by myometritis and endometrial vasculitis and decrease in the dam's progesterone levels.

## **DIAGNOSIS**

The diagnosis of EVA is based on the demonstration of clinical signs, lesions, an etiologic agent, and/or seroconversion. A presumptive diagnosis of EVA cannot be based solely on the nature of the clinical signs of disease. The detection of the seroconversion with complement-dependent virus neutralization performed with the Bucyrus strain in EAV-infected animals is a reliable method used to identify EAV infection in horses and in abortion. Some foals have presuckle positive serology tests for EVA, which suggests *in utero* infection. Postsuckle testing would be invalid because of passive transfer of maternal immunity in seroconverted mares. Tissue culture cell lines generally used to isolate EAV are RK-13 cells, Vero cells, and equine lung cells.

Appropriate specimens for virus isolation from the live

animal include nasopharyngeal swabs or washing, conjunctival swabs, and citrated ethylenediaminetetraacetic acid (EDTA) or heparinized blood samples. Indirect immunohistochemistry can be used to detect the infection *in vivo* in cases with dermatitis and permits the *post mortem* identification of EAV within the cytoplasm of epithelial cells—such as alveolar pneumocytes, enterocytes, adrenocortical cells, trophoblast, thymus stroma, renal tubular cells, and male accessory genital glands. EAV also can be demonstrated within endothelia or in vascular, myometrial, and cardiac myocytes; macrophages; dendritic cells of lymphoid organs; and chorionic mesenchymal stromal cells. Other molecular techniques, such as reverse transcriptase-polymerase chain reaction (RT-PCR), have been used to identify the presence of EAV, especially in regard to genital transmission of the virus. The application of these techniques to identify viral RNA in tissues may be useful for diagnostic purposes and further studies, although sensitivity and specificity for routine diagnostic use still require evaluation.

Detection of the carrier state in the stallion initially involves the collection of a blood sample to determine the EAV serologic status of the horse. Only horses that test positive at a serum dilution of 1:4 or greater without an appropriately certified vaccination history against EVA need to be considered potential carriers of the virus. These sires should be tested virologically by attempting isolation of EAV *in vitro* from a collection of semen or by identifying EAV in semen by RT-PCR. A more expensive and slower—but very reliable—alternative is to test-breed the suspect stallion to two seronegative mares and evaluate them for seroconversion to EAV up to 28 days after breeding. Because carriers constantly shed the virus in semen, virus identification can be attempted at any time from a potential carrier sire. The collection must contain the sperm-rich fraction of the ejaculate.

Several infectious and a few noninfectious diseases should be considered differential diagnoses for EVA. These diseases include rhinopneumonitis (equine herpesviruses 1 and 4), influenza (orthomyxoviruses A equi 1 and 2), equine infectious anemia, African horse sickness (orbivirus), Hendra disease (retrovirus), Getah virus (togavirus), purpura hemorrhagica, and the toxic plant Hoary alyssum (*Berteroa incana*). Amongst differential diagnoses it is necessary also to include infectious and noninfectious causes of abortion.

## **TREATMENT AND PREVENTION**

With rare exceptions, horses naturally infected with EAV make uneventful clinical recoveries, even in the absence of symptomatic treatment. Mortality in natural cases is rather uncommon and is mainly reported in neonatal foals affected by severe acute bronchointerstitial pneumonia.

Isolation of horses that exhibit clinical signs is paramount to decrease the spread of EAV, which is easily diffused by fomites. Colostrum from mares infected at or around the time of parturition should be discarded for that parturition only. General supportive care should include a thoroughly ventilated and protected environment. Nonsteroidal antiinflammatory drugs (NSAIDs) can be used to decrease the high fever and stimulate the horses to

eat. Treatment of one foal with hyperimmune plasma collected from a horse with a very high titer to EVA was attempted but was performed late in the course of the disease and was not effective. Earlier intervention with specific passive transfer of immunity to EVA in the case of neonatal disease might be beneficial, given that adequate colostral passive transfer of immunity appears to be protective. Rest should be mandatory for a minimum of 1 week after the clinical signs have resolved. A convalescent period of 3 to 4 weeks is needed for a complete resolution of an uncomplicated viral respiratory problem. If after culture of the airway secretions a bacterial agent is identified, the isolate should be tested for antimicrobial sensitivity; appropriate therapy then should be initiated. Common secondary bacterial pathogens are *Streptococcus equi* subsp. *zooepidemicus* and *Escherichia coli*.

A modified live vaccine against EAV is licensed and available in North America and was used effectively to help control the 1984 outbreak of EVA in Kentucky. The vaccine was developed to prevent infection and establishment of the carrier state in previously unexposed sires and to protect the breeding of nonpregnant mares with carrier sires. Annual revaccination of breeding sires 28 days before the beginning of the breeding season prevents the occurrence of the EAV carrier state. Mares that are bred to carrier sires should be vaccinated annually at least 21 days before breeding. Because vaccinated mares may shed the virus transiently after being bred to a carrier stallion, these

mares should be isolated for 21 days after breeding. The vaccine should not be used in pregnant mares—especially during the last months of gestation—nor in foals under 6 weeks of age; exceptions are emergencies when the risk of exposure is high, such as a herd outbreak situation with foal mortality in foals born to seronegative mares. Foaling mares should be vaccinated after foaling and before being rebred.

Regulations and recommendations for the management and breeding of EVA carrier sires vary by state. Import and export regulations vary by country.

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## CHAPTER 2.2

# Equine Herpesvirus

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*Kennett Square, Pennsylvania*

**H**erpesvirus infections are extremely common in the equine population. In one survey of young horses, 100% had serologic evidence of infection with equine herpesvirus EHV-4, which is a major cause of upper respiratory tract disease. Infection with EHV-1 is less common, and in addition to causing clinical signs similar to EHV-4 infection, it is responsible for the devastating and unpredictable abortion, fatal neonatal illness, and myeloencephalopathy. The pathogenic potential of EHV-2 is unclear; however, most horses have serologic evidence of exposure. EHV-2 is commonly isolated from the blood of healthy foals and from airway secretions from foals with respiratory tract disease. Coital exanthema is a venereal disease caused by EHV-3. Vesicular lesions appear on the penis and prepuce of the stallion and on the vulvar mucosa of the mare.

EHV infections of the respiratory tract are prevalent, highly contagious, and performance-limiting and thus are

economically important. Abortion and myeloencephalopathy are less common but are economically significant due to high mortality.

Control of EHV infection has been difficult due to the presence of latent infections that may reactivate without clinical signs and produce viral shedding. Furthermore, EHV-1 can evade the immune system and induce immunosuppression. Immunity after natural infection or vaccination is brief, and horses may be repeatedly infected during their lifetime.

### RESPIRATORY DISEASE

#### Clinical Signs

The severity of clinical signs associated with EHV infection depends on the age of the horse, previous EHV infection or vaccination, stress, concurrent illness, viral strain,

eat. Treatment of one foal with hyperimmune plasma collected from a horse with a very high titer to EVA was attempted but was performed late in the course of the disease and was not effective. Earlier intervention with specific passive transfer of immunity to EVA in the case of neonatal disease might be beneficial, given that adequate colostral passive transfer of immunity appears to be protective. Rest should be mandatory for a minimum of 1 week after the clinical signs have resolved. A convalescent period of 3 to 4 weeks is needed for a complete resolution of an uncomplicated viral respiratory problem. If after culture of the airway secretions a bacterial agent is identified, the isolate should be tested for antimicrobial sensitivity; appropriate therapy then should be initiated. Common secondary bacterial pathogens are *Streptococcus equi* subsp. *zooepidemicus* and *Escherichia coli*.

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### RESPIRATORY DISEASE

#### Clinical Signs

The severity of clinical signs associated with EHV infection depends on the age of the horse, previous EHV infection or vaccination, stress, concurrent illness, viral strain,

and dose. Typical signs include fever ( $102^{\circ}$ – $106^{\circ}$  F for 2–5 days), inappetence, lethargy, cough, and serous nasal discharge that may become mucoid. Occasionally a biphasic febrile response results in a second episode of fever after 2 to 3 days of normal temperatures. In contrast to equine influenza, cough is not as prominent a feature of EHV infection; however, a cough may be induced by tracheal compression or may occur during deep inspiration with a rebreathing bag in place. Mandibular lymph nodes become mildly enlarged and painful. Distal limb edema occurs infrequently. “Silent” infections occur without clinical signs. Furthermore, horses with partial immunity may experience fever and mild inappetence without evidence of respiratory disease. Clinical pathology reveals lymphopenia, neutropenia, and hyperfibrinogenemia.

Given the immunosuppressive quality of EHV infection, some horses may develop a syndrome of performance-limiting inflammatory airway disease after clinical signs of the acute phase of infection have resolved. Other complications of EHV infection include exercise-induced pharyngeal dysfunction secondary to upper respiratory tract inflammation.

In addition to EHV-1 and -4, increasing evidence shows that EHV-2 is a respiratory pathogen in foals. This virus is isolated more frequently from tracheal secretions of foals with respiratory disease than from healthy foals. It is ubiquitous on some farms and can be isolated from the peripheral blood of most foals. Clinical signs associated with EHV-2 infection in 1- to 8-month-old foals include fever, keratoconjunctivitis, cough, mucopurulent nasal discharge, mandibular lymphadenopathy, and abnormal lung sounds. Researchers have proposed that EHV-2 infection may be a predisposing factor for *Rhodococcus equi* pneumonia; however, the relationship between these two pathogens has not been fully elucidated.

## Diagnosis

A fourfold increase in virus-neutralizing (VN) or complement-fixing (CF) antibody titer is diagnostic of EHV infection. However, this increase may be difficult to demonstrate, as titers rise rapidly during infection and may be increased at the onset of clinical signs. Cross-reaction between EHV-1 and EHV-4 may occur with CF and VN assays, but specific ELISA is available.

The virus may be isolated from nasopharyngeal swabs or from citrated or heparinized whole blood for approximately 12 days after infection. Nasopharyngeal samples are obtained with a sterile 2-inch  $\times$  2-inch gauze attached to a twisted stainless steel wire or a uterine infusion pipette. The gauze then is placed in virus transport media and refrigerated or frozen during transportation to the laboratory.

Polymerase chain reaction (PCR) is a sensitive, rapid, and inexpensive diagnostic method that is now available for clinical use. Nasal swabs and whole blood collected with ethylenediaminetetraacetic acid (EDTA) as an anticoagulant should be submitted.

## Treatment and Control

Most uncomplicated EHV respiratory infections resolve spontaneously within a few weeks. Rest is an important

component to recovery and should continue until coughing, nasal discharge, and abnormal lung sounds have resolved. EHV-1 induces immunosuppression, and infected horses should be monitored for secondary bacterial infections. Some horses develop persistent lower airway inflammation that is manifested by exercise intolerance, persistent cough, and abnormal lung sounds after viral respiratory infection. This syndrome should be differentiated from bacterial pneumonia or bronchitis by evaluation of specimens obtained via tracheal aspiration. Ceftiofur (2.2 mg/kg IM q24h) or trimethoprim-sulfamethoxazole (25 mg/kg PO q12h) is appropriate in the initial treatment of secondary bacterial infections.

Because herpesvirus infections create immunosuppression and have the ability to evade the immune system, immunomodulators may be an appropriate adjunctive therapy. The intravenous administration of inactivated *Propionibacterium acnes* (EqStim) is an effective immunomodulator in healthy horses, but rigorous clinical trials have not been conducted to document its efficacy in the treatment of viral respiratory disease. Although it is not absorbed after oral administration, interferon-alpha (50 U PO q12h for 5 days) reduces lower airway inflammation in racehorses, perhaps through stimulation of pharyngeal lymphoid tissues.

Vaccination against EHV-1 and -4 decreases the duration and severity of disease but does not consistently prevent infection or shedding of the virus. Furthermore, the duration of immunity is short; therefore vaccination at 3- to 4-month intervals is recommended for horses at high risk of infection. Primary vaccination of foals should begin at 4 to 6 months of age, with three doses at monthly intervals.

## MYELOENCEPHALOPATHY

Equine herpesvirus myeloencephalopathy (EHM) is a common cause of central nervous system (CNS) disease in the horse. The vast majority of EHM is caused by EHV-1; it is rarely associated with EHV-4. Although a herpesvirus strain associated with myeloencephalopathy has not been clearly demonstrated, restriction enzyme analysis has shown similarities among isolates from outbreaks of EHM. Viral recrudescences or inhalation of virus and infection of respiratory epithelium leads to viremia. Infection of CNS vascular endothelium results in thrombosis and ischemic myeloencephalopathy. The involvement of the immune system has been implicated by the lack of clinical signs in foals that have not been previously infected with EHV.

## Clinical Signs

Multiple horses in a herd often are affected by EHM; however, sporadic individual cases are reported. A history of contact with horses demonstrating signs of herpesvirus disease is common. Fever, lethargy, and inappetence of 1 to 3 days' duration occur 1 to 6 days before an acute onset of neurologic signs. Not all horses that become infected during an outbreak develop EHM. Symmetric hind limb ataxia and paresis, bladder atony, fecal retention, and recumbency are the most common clinical signs of EHM. Other clinical signs include lower limb edema, blindness,

head tilt, tongue weakness, nystagmus, and perineal sensory and motor deficits. Ocular lesions such as serous discharge, mydriasis, hypopyon, uveitis, chorioretinitis, retinal detachment, retinal hemorrhage, and blindness are rare. A wide range of severity exists from mild ataxia to recumbency and death. Neurologic deficits generally stabilize 24 to 48 hours after the onset of signs and then slowly improve during the following weeks to months.

### Diagnosis

Cerebrospinal fluid (CSF) of horses with EHM demonstrates an increased total protein with little or no change in nucleated cell concentration. The presence of this dissociation between albumin concentration and cytology, in conjunction with characteristic clinical signs, strongly supports the diagnosis. The magnitude of abnormalities in the CSF does not appear to correlate with clinical signs or prognosis. Cytologic examination of CSF reveals primarily mononuclear cells. CSF frequently has a yellow discoloration (xanthochromia) associated with red blood cell breakdown. Isolation of virus from CSF is rare. Serologic, PCR, and virus isolation techniques used to diagnose EHV respiratory disease are appropriate for the diagnosis of EHM.

### Treatment

Corticosteroids (dexamethasone 0.05 to 0.10 mg/kg IV or IM q12h) have been advocated in the treatment of EHM. The antiinflammatory properties of corticosteroids must be weighed against the detrimental effects on immune function and the possibility of inducing laminitis. Evaluating the efficacy of corticosteroids is difficult, given the natural course of this disease. Although the efficacy of dimethyl sulfoxide (DMSO; 1 g/kg diluted in saline to a 10% solution IV q24h for 3 days) in the treatment of EHM has not been evaluated, its reported ability to inhibit platelet aggregation and scavenge free radicals supports its continued use. Flunixin meglumine (1.1 mg/kg IV q12h) is indicated for CNS vasculitis.

Good nursing care is essential in the management of recumbent horses. During outbreaks of EHM, horses may be managed on the farm of origin. Recumbent horses should be kept in a sternal position as much as possible or maintained in a sling. Antimicrobial therapy (trimethoprim-sulfamethoxazole 25 mg/kg PO q12h or ceftiofur 2.2 mg/kg IM q12h) is indicated in severe cases because corticosteroid-induced immunosuppression, urinary catheterization, and decubital ulcers all can lead to secondary bacterial infection. Hydration and nutrition should be monitored closely in dysphagic horses. When bladder atony is present, urinary catheterization should be performed at least twice daily. Recumbent or tractable ambulatory horses may tolerate indwelling Foley catheters (24-28 French) attached to a closed system or Heimlich valve.

Acyclovir (10 mg/kg PO 5 times daily) has been advocated in the treatment of EHV infection; however, evidence suggests that it is not effective against EHV-1, and pharmacokinetic studies in the horse are lacking. Penciclovir is effective *in vitro* against EHV-1, but there are no reports of its use in horses. Renal function should be monitored during treatment with acyclovir.

### Prognosis

In general, the prognosis is related to the severity of clinical signs and initial response to treatment. The prognosis for a recumbent horse that cannot stand with assistance is grave. Many horses that develop severe hind limb ataxia and survive have residual deficits that prevent their return to athletic function. Those with mild deficits may regain athletic function.

### Prevention and Control

Reports of naturally occurring outbreaks of EHM have suggested that narrow gaps between fields may be enough to prevent transmission of the virus between horses. Horses should be maintained in their same groups and then segregated if possible. The ability to accurately identify and segregate infected horses during an outbreak will improve with the availability of rapid and specific tests such as PCR.

Vaccination during an outbreak is controversial. Currently available vaccines do not claim prevention of EHM. Vaccination reduces viral shedding but does not prevent infection. Because previous exposure to EHV-1 or -4 may be a risk factor for EHM, this author does not advocate vaccination during an outbreak.

### ABORTION

Abortion caused by EHV occurs worldwide and is the most important cause of infectious abortion in the mare. Abortion storms are usually associated with EHV-1; however, EHV-4 is associated with sporadic abortion. Infection occurs by inhalation of virus particles or recrudescence of latent infections during periods of stress. Evidence of respiratory disease may be absent in aborting mares. Viremia leads to infection of the fetus or vasculitis of the endometrium. In most cases the aborted fetus is highly infectious and an important source of virus for other mares; however, the fetus can be virologically negative when it is rapidly expelled after widespread endometrial inflammation.

### Clinical Signs

Abortion of a fresh fetus without premonitory signs is characteristic of EHV infection. The placenta is normal or mildly edematous and is passed with the fetus. Gross lesions include meconium staining, pulmonary edema, jaundice, petechiae, subcutaneous edema, splenic enlargement, and excess peritoneal and pleural fluid. Numerous white to gray 5-mm areas of necrosis are present in the liver. The fetus, which is highly contagious, should be removed in a plastic bag to prevent it from contaminating the environment. *Post mortem* examinations conducted on the farm should be performed in an area that can be effectively disinfected. Phenolic disinfectants are effective against EHV and are not inactivated by organic debris.

Abortion occurs from 2 weeks to several months after exposure to virus. The vast majority of mares that abort because of infection are in the last 4 months of gestation. Sporadic abortions of one or two mares in a herd are most common; however, abortion storms may affect more than half the herd.



## Diagnosis

Serologic diagnosis is problematic because infection may precede abortion by several weeks and because recrudescence may not induce an antibody response. If a fresh fetus cannot be submitted to a diagnostic laboratory, frozen paired samples of lung, liver, thymus and adrenal gland should be submitted in formalin. Fluorescent antibody staining, immunohistochemistry, and virus isolation of fetal tissues can confirm the diagnosis.

## Treatment and Control

Immunity is short-lived, and mares are not immune to future herpesvirus abortions. The virus is rapidly cleared from the reproductive tract. If the abortion is not complicated, fertility is not compromised, and specific treatment is not indicated.

The major source of EHV is aerosolized respiratory secretions, and therefore horses that display signs of respiratory disease should be isolated. Because of the high prevalence of EHV infection in young horses, late gestational mares should be separated from mares with foals, weanlings, yearlings, and transient horses. Mares should be separated into small groups based on stage of gestation. Stress may induce recrudescence of latent virus; therefore late gestational mares should not be transported long distances. Vaccination has decreased the incidence of herpesvirus abortions, but abortion remains possible in vaccinated mares. Pregnant mares should be vaccinated during the fifth, seventh, and ninth months of gestation with an inactivated vaccine licensed for the prevention of EHV abortion. Many veterinarians also advocate vaccination during the third month of gestation. Vaccination in the face of an abortion outbreak may prevent infection in horses that have not yet been exposed.

Once a mare has aborted, all members of the foaling herd should remain on the farm until they have foaled, because the duration between infection and abortion can be several months. If the mare has aborted in a stall, the area should be disinfected, and the bedding should be burned. Other horses on the farm should remain on the farm until 1 month after the last abortion. Any horses that have left the farm around the time of a suspected herpesvirus abortion should be isolated from late gestation mares. Segregating mares into small groups after an abortion may be helpful in limiting the spread of disease.

## COITAL EXANTHEMA

Equine coital exanthema occurs worldwide and is caused by EHV-3. This highly contagious but self-limiting venereal disease results in vesicular lesions on the penis and prepuce of stallions and on the vulvar mucosa of mares. Inapparently infected mares may transmit the virus to stallions. Stallions appear to be more severely affected than mares, and clinical signs include lethargy, anorexia, and fever. Mild infections occur and may go undetected. Approximately 2 to 5 days after exposure, vesicles appear first on the penis and then on the prepuce. Vesicles become pustules and then slough, thus resulting in ulcerations up to 1.5 cm in diameter. Healing occurs within a month, but depigmented areas may remain. Mares de-

velop similar erosions on the vulvar mucosa and perineal skin that progress to scabs and heal. Occasionally lesions are present on the skin around the lips and nostrils and on the conjunctiva. The muzzle of a foal that suckles an infected mare may be similarly affected. Although transmission occurs primarily through breeding, iatrogenic transmission by contaminated equipment also can occur.

Latent infections probably exist, but reinfections also can occur without clinical signs. Recrudescence may occur in aged broodmares that display clinical signs during late gestation. Diagnosis can be made based on clinical signs and history. Antibody titers peak 2 to 3 weeks after infection. VN antibody may be present for more than a year, whereas CF antibody is present for only 2 months after infection. The virus can be isolated from erosions present during the acute infection.

Although infection does not appear to affect conception or maintenance of pregnancy, some stallions may be reluctant to breed mares, and many veterinarians recommend that stallions breed only after lesions have healed. The use of an open-ended artificial vagina and artificial insemination may reduce the chance of virus transmission. Treatment of lesions with topical antibiotic ointments helps prevent secondary infections.

## PERINATAL EQUINE HERPESVIRUS-1 INFECTION

### Clinical Signs

Infection of the mare during late gestation with EHV-1 may result in a syndrome of severe neonatal illness. In most reports of perinatal EHV infection, evidence exists of EHV-related disease, including abortion or myeloencephalopathy, on the farm; however, sporadic cases occur. Foals may be born weak or apparently normal. Clinical signs appear within 48 hours of birth and include respiratory distress, weakness, icterus, fever, tachycardia, and, in some cases, diarrhea. The majority of foals that develop these clinical signs and are infected with EHV-1 in the perinatal period die, and those that survive require intensive care. Leukopenia characterized by a left shift, neutropenia, and severe lymphopenia suggest EHV-1 perinatal infection. In some cases, liver enzymes are elevated.

### Diagnosis

Foals that survive EHV-1 infection may not seroconvert; however, the virus can be isolated—and presumably identified by PCR—from peripheral blood mononuclear cells. *Post mortem* lesions include interstitial pneumonia, thymic necrosis, and adrenocortical hemorrhage. Infection can be confirmed by virus isolation from fetal tissues or by identification of EHV-1 antigen by immunohistochemistry.

### Treatment

Affected foals usually need intensive nursing care, respiratory support, intravenous fluids, antimicrobials, and nonsteroidal antiinflammatory drugs (NSAIDs). Acyclovir (8-16 mg/kg PO q8h) has been reported in the treatment of neonatal EHV-1 infection; however, acyclovir is ineffective

against EHV-1 *in vitro*. Little information exists on the pharmacokinetics and activity of this medication in neonatal foals.

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## CHAPTER 2.3

# Equine Influenza

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Equine influenza is the most commonly diagnosed viral respiratory disease of the horse. It has a worldwide distribution but has not been reported in Iceland, New Zealand, or Australia.

Equine influenza virus (EIV) is a single-stranded RNA virus (orthomyxovirus). Only type A influenza viruses are known to infect horses. They are prone to mutation and constant "drift," or change in antigenicity. Periodically these changes in antigenicity occur in the form of a sudden and dramatic "shift." The antigenicity of the virus depends principally on the two major proteins studded on the outer surface of the virus—hemagglutinin (HA) and neuraminidase (NA). Part of the nomenclature of the viruses is based on these surface proteins. All currently circulating strains are believed to be of the H3N8 type. At the present time, EIV appears to evolve along two branches—European and North American—of a phylogenetic tree.

Equine influenza is a highly infectious and contagious disease. Outbreaks commonly occur amongst large groups of susceptible horses. Frequently these are groups of racehorses, with those 2 to 3 years of age suffering the highest morbidity. The disease is capable of rapid spread through populations of naïve animals. However, outbreaks may proceed more slowly when the affected group comprises animals with varying histories of previous exposure to the virus or vaccines. Typically, such outbreaks last about 30 days and follow a symmetric epidemic curve that peaks at about day 15 and results in clinical disease in 15% to 30% of the animals in the group. Several epidemiologic studies indicate that in those regions where the disease is endemic, such outbreaks may occur annually. The timing of these outbreaks seems specific to each population and depends on a number of risk factors. Epidemics are thought to follow the introduction of an infected—perhaps subclinically affected—animal into a susceptible population. The susceptibility of the population is related to its age structure and the length of time since exposure to natural

infection or an efficacious vaccine. Additional risk factors include movement and commingling of horses from several sources, close confinement of animals, and high percentages of young susceptible animals within individual training or management groups. The fatality and severe complication rates are generally very low. The principle economic impact of these outbreaks relates to the 2- to 3-week withdrawal of affected horses from regular training and performance schedules.

Influenza virus is not capable of prolonged survival in individual animals or the environment. Transmission of the virus among horses occurs via direct contact with nasal secretions, by the aerosol route (coughing), or through contact with recently contaminated fomites—including feed, water, equipment, and clothing. After a susceptible animal is infected, the virus invades the epithelial cells that line the respiratory tract and induces pathologic change along its full length. Within one day of infection, the virus causes destruction and desquamation of both the ciliated and the mucous-producing cells of the respiratory tract, exposure of the basal layer, and loss of normal mucociliary clearance of the lower respiratory tract. Within 48 hours of experimental infection, the nasal mucous turns purulent, and high concentrations of *Streptococcus zooepidemicus* can be isolated from these secretions.

Experimentally, viral shedding peaks on day 2 postinfection and ceases by day 8 or 9. The protective immune response is associated with the development of antibodies against the HA and NA glycoproteins. The production of mucosal antibody, serum antibody, and cellular immunity all develop after an active infection with the virus.

### CLINICAL SIGNS AND MANAGEMENT

The principal clinical signs of EIV include fever, coughing, and mucopurulent nasal discharge. Affected horses may

against EHV-1 *in vitro*. Little information exists on the pharmacokinetics and activity of this medication in neonatal foals.

### Supplemental Readings

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Experimentally, viral shedding peaks on day 2 postinfection and ceases by day 8 or 9. The protective immune response is associated with the development of antibodies against the HA and NA glycoproteins. The production of mucosal antibody, serum antibody, and cellular immunity all develop after an active infection with the virus.

### CLINICAL SIGNS AND MANAGEMENT

The principal clinical signs of EIV include fever, coughing, and mucopurulent nasal discharge. Affected horses may

also experience malaise, inappetence, and dyspnea. After experimental infections the clinical signs do not become evident until day 2 postinfection. Rectal temperatures frequently increase to between 38.9° and 41.4° C, with a secondary peak occurring at approximately day 5 or 6 postinfection. Left untreated, fever may persist until day 10 to 14. Coughing and mucopurulent nasal discharge become evident by day 2, peak and remain high until about day 10, and then gradually return to normal around day 21. Experimentally infected animals may lose significant amounts of weight during the course of the disease.

After natural disease a variety of complications—including bacterial pneumonia, pleuropneumonia, persistent coughing, limb edema, and increased incidence of heaves—has been reported anecdotally, but research supporting these assertions has not been published.

Basic clinical management includes rest or limited exercise until the respiratory epithelium has had the opportunity to heal completely, adequate shelter, and an environment and feed source that is as free of dust as possible. The role of treatment in the management of equine influenza is not clear. Without any treatment, animals recover normally over a period of 1 to 3 weeks. Judicious use of nonsteroidal antiinflammatory drugs (NSAIDs) and antibiotics logically hasten the resolution of fever and nasal discharge and may limit weight loss, but no published data support this contention. Other treatments, including expectorants and bronchodilators, have not been shown to be of benefit. The use of corticosteroids and cough suppressants is probably contraindicated. Corticosteroids are immunosuppressive, and recovery from the disease highly depends on an appropriate immunologic response. Cough suppressants likely reduce clearance of respiratory tract secretions, bacteria, and inflammatory and cellular debris. Antiviral agents (e.g., rimantadine hydrochloride) that are administered at the time of initial infection may limit the severity and duration of signs. However, these drugs are not registered for use in the horse and are presently too expensive for general application.

## DIAGNOSIS

The diagnosis of equine influenza is based on the appearance of typical clinical signs and the results of laboratory tests. Although the sudden appearance in a group of young horses of paroxysmal coughing, high fever, and mucopurulent nasal discharge in the absence of severe lymphadenopathy strongly suggests EIV, appropriate laboratory tests are essential to differentiate this disease from other causes of inflammation of the equine respiratory tract. Because of the ability of the disease to spread rapidly within the group, the more quickly the diagnosis can be confirmed, the sooner appropriate action can be taken to limit its spread.

At least two point-of-care rapid human influenza diagnostics tests are being used to confirm diagnosis in horses. These tests are available as kits suitable for testing nasal swab samples obtained from individual horses. The tests can be performed in the field, under very simple conditions, and yield a result within 30 minutes. Although serologic tests (HA inhibition and single radial hemolysis) have

important roles in confirming the diagnosis, the interval between collection of acute and convalescent samples is too long for these results to provide information useful to control an acute outbreak of the disease. Virus isolation is considered pathognomonic for the presence of disease but is a lengthy and expensive process that frequently fails to detect the virus in naturally infected animals.

## PREVENTION

Given the difficulty in altering the course of the disease once animals become infected, most efforts to deal with EIV should be aimed at preventing outbreaks and minimizing their severity and duration when they do occur. Vaccination, quarantine, early detection of animals shedding live virus, and hygiene are all important in the control of this disease.

A variety of efficacious vaccines against equine influenza, including both inactivated and modified live vaccines, have been developed and marketed. The inactivated vaccines include killed whole virus vaccines, immune-stimulating complexes (ISCOMs), and subunit vaccines. In compliance with recommendations from the Office International des Epizooties (OIE), updated versions of some of these vaccines contain antigen (H3N8) derived from both North American and European strains of the virus. Existing data suggest that these vaccines achieve their effect principally through stimulation of the production of antibody against the HA surface protein.

A temperature-sensitive, cold-adapted, modified live intranasal vaccine has been developed and is now marketed in the United States and Canada. It was developed by attenuating a field strain of the virus, A/equi/Kentucky/1/91(H3N8) with the same technology that has been used to produce a new human influenza vaccine. The vaccine protects naïve animals 11 months of age and older against both North American and European strains of the virus. Protection is achieved after a single application of the vaccine, and efficacy has been examined and proven in several independent challenge trials.

EIVs are prone to genetic and antigenic change over time. These changes can be dramatic and lead to marked antigenic shift and pandemics of disease, as occurred with the sudden appearance of the H3N8 strain in Miami in 1963. However, these changes usually occur as the result of genetic substitution and selective pressure and bring about the gradual antigen drift noted with the yearly identification of slightly different strains of the virus. The process occurs more slowly for equine than human strains but still makes necessary the periodic updating of the commercial vaccines to help ensure their continued efficacy. Some data show that the more closely the vaccine strain is related to circulating wild-type virus, the more effective the vaccine; however, the frequency with which the vaccines must be updated has not been clearly established. Fortunately, the rate of drift of equine influenza viruses is slow enough to permit vaccination to stimulate a useful protective response even when the interval between the isolation of the vaccine and challenge strains is several years.

Equine influenza vaccines help prevent disease; they do not provide complete protection of all currently vaccinated

individuals in a population. Many published reports address outbreaks of disease in vaccinated animals. Reasons for vaccine failure arise from a number of circumstances—including unrealistic expectations, suboptimal vaccination programs, use of outdated antigens, and variation of individual vaccines in their ability to provoke a protective immune response. In addition, a small but significant percentage of animals do not respond to these vaccines as part of normal biologic variation.

To be effective, vaccination programs must be based on a sound strategy that accounts for the epidemiology of the disease, that is specifically designed for each group of horses, and that is aimed at achieving herd immunity. To achieve this effectiveness, all horses in the group or population must be vaccinated. Vaccinating a few animals within a susceptible group may not be of much benefit to those individuals or the group. Vaccination programs should be completed at least 3 weeks before a period of high risk. The number of vaccinations per year should be based on the number of anticipated periods of high risk and the duration of immunity of the vaccine. Because of frequent reports of disease among vaccinated horses, only those vaccines for which acceptable challenge or field trial data have been published in peer-reviewed scientific reports should be used. Given that other infectious diseases of horses do not share the same epidemiologic risk factors and patterns of this disease, the use of monovalent vaccines is likely to be most appropriate. Prevention and control of other important infectious diseases of horses, such as tetanus and strangles, should be achieved through separate and independent vaccination programs.

Outbreaks of influenza have not been reported in foals, and animals younger than approximately 9 months of age may not respond well to vaccination. Three or more vaccinations are required to achieve an adequate immune response among naïve animals with inactivated vaccines. Naïve horses develop a protective immune response against experimental challenge after a single dose of the modified live intranasal vaccine.

New introductions of horses must be adequately vaccinated and should not be commingled with an established population before an isolation period of 14 days. Nasal swabs and serum samples should be collected from any

animal that develops signs of respiratory disease during this period. The remainder of the new group, particularly those 3 years of age and younger, then should be closely examined for any signs consistent with equine influenza (fever, cough, or nasal discharge). Any animal with one or more of these signs should be sampled. The nasal swabs should be examined with a rapid test suitable for immediate detection of influenza virus. Positive swabs should be shipped on ice to the nearest veterinary laboratory or OIE equine influenza reference center (e.g., Gluck Center, University of Kentucky, Lexington, Ky.) for virus isolation and typing. By following this practice, veterinary practitioners will facilitate the process of documenting the evolution of the virus and aid in the appropriate updating of the vaccines. Animals suspected or shown to be shedding live virus should be placed in suitable quarantine for 14 days. Convalescent serum samples should be collected 14 days later and submitted for hemagglutination inhibition (HAI) or single radial hemolysis (SRH) tests to determine both acute and convalescent titres to EIV.

The population into which the horses are being introduced also should be observed closely. Samples should be collected from any animal that develops signs of disease. If more than 5% of the target population develops signs consistent with EIV, revaccination of the entire herd or group should be considered.

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## CHAPTER 2.4

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# Equine Infectious Anemia

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**E**quine infectious anemia virus (EIAV), the agent of equine infectious anemia (EIA), is a member of the subfamily Lentiviridae, of the family Retroviridae. All retroviruses contain the genes *gag*, *pol*, and *env*, which encode the viral structural proteins and enzymes important for replication. Lentiviruses contain additional genes that are required for virus persistence and pathogenesis.

A feature unique to the retrovirus is its ability to convert its genetic material RNA to a DNA intermediate by using virally encoded reverse transcriptase. A different virally encoded enzyme, integrase, catalyzes the integration of the DNA intermediate into host chromosomal DNA, where it remains as the provirus. The provirus then uses different aspects of the host cell to replicate its genome, manufacture viral proteins, and assemble the virally encoded proteins into virions, which then bud from the host cell. The important clinical outcome of this viral replicative strategy is that lentiviruses become integrated into the host genome and are never entirely eliminated by the host. Ongoing viral replication occurs at some level throughout the life of the host. Additionally, the lentiviral reverse transcriptase is highly error-prone, and virus replication is associated with the introduction of mutations to the virus itself. Those mutations that are not deleterious to the virus are maintained. Therefore a heterogeneous population of related variants mediates lentiviral infection.

EIAV is closely related to other lentiviruses of both veterinary and human importance. These include feline immunodeficiency virus (FIV), bovine immunodeficiency virus (BIV), caprine arthritis-encephalitis virus (CAEV), maedi-visna virus of sheep, simian immunodeficiency virus (SIV), and human immunodeficiency viruses types 1 and 2 (HIV-1 and -2). Animal lentiviruses continue to play important roles in research aimed at understanding the biology and pathophysiology of HIV.

Lentiviruses are generally associated with chronic, progressive diseases of insidious onset of the hematologic and neurologic systems of animals and humans. In contrast, the onset of clinical disease produced by EIAV infection is usually rapid, with clinical signs that occur within 1 to 4 weeks. However, clinical outcome to infection is variable and is probably due to host factors, the virulence of the virus strain, and the infecting dose. Consequently, EIAV infection may result in subclinical disease or in clinically apparent disease that ranges from mild to severe.

### CLINICAL SIGNS

Infection of horses, donkeys, and mules with EIAV may result in very different manifestations. Many equids never

show obvious clinical signs. Horses that develop overt disease may progress through three different stages: acute, chronic, and inapparent carrier. The severity and duration of clinical signs may vary in the acute and chronic stages. The acute stage of disease is associated with the initial viremic burst and usually occurs within 1 to 4 weeks of infection. Common findings in acutely infected animals include high fever (up to 107° F, 41.6° C), thrombocytopenia, depression, and inappetence. Severely thrombocytopenic horses may develop mucosal petechiations, epistaxis, and ventral pitting edema that may be fatal. Most horses, however, survive the acute stage and undergo a brief recovery period (5 to 30 days), during which levels of viremia decrease substantially and clinical signs resolve.

The chronic stage follows and is characterized by recurring and intermittent cycles of viremia, fever, thrombocytopenia, and depression, which typically decrease in severity over approximately 1 year. The recurrent nature of the disease is, in part, due to antigenic viral variants that are not recognized by the immune system. Temporary escape from the immune response allows higher replication of that variant. Horses may survive the chronic stage of disease and progress to the inapparent carrier stage, die during the recurrent disease episodes (as during the acute stage), or progress to a debilitating form of the disease characterized by ill-thrift, anemia, ventral pitting edema, progressive weight loss, and ultimately death.

Progression to the inapparent carrier stage is temporally associated with development of strong humoral and cell-mediated immune responses. However, despite mounting a strong immune response, infected horses are unable to clear the virus and remain infected for life. The level of virus replication that occurs in inapparent carriers is sufficient for transmission of virus and may be lethal to the newly infected horse. Administration of immunosuppressive drugs, such as corticosteroids, may precipitate viral replication and clinical disease in inapparent carriers.

The clinicopathologic findings of EIAV vary by the stage of disease and largely reflect activation of the host immune response. Thrombocytopenia is the most consistent finding and is mediated by immunoglobulin G (IgG) and immunoglobulin M (IgM) binding to platelets, with subsequent removal from the circulation by tissue macrophages of the liver, spleen, and lymph nodes. Additionally, it is believed that circulating platelets are activated and hypofunctional. Activated platelets can aggregate or degranulate—events that lead to removal of platelets from the circulation. The anemia variably associated with chronic recurrent disease and commonly associated with the chronic and debilitating form of disease

is due to several mechanisms. The virus is capable of inhibiting bone marrow erythropoiesis. Additionally, virus or virus-antibody complexes may adsorb to erythrocytes, activate complement, and result in intravascular hemolysis. Furthermore, complement-coated erythrocytes may be phagocytosed, thus resulting in extravascular hemolysis. Hemolytic anemia, if severe, may result in hyperbilirubinemia and icterus. The Coombs' test, which detects the presence of antibodies on the surface of erythrocytes, may be positive during episodes of disease. Inclusion of complement-specific antibodies enhances detection. Increases in erythrocyte lactate dehydrogenase and glucose-6-phosphate dehydrogenase reflect a regenerative bone marrow response to anemia. A nonspecific hypergammaglobulinemia is also documented in most horses, including inapparent carriers. Mild leukopenia, lymphocytosis, and monocytosis may be associated with active disease.

Horses that die of clinically severe EIAV infection may have the following necropsy findings that reflect the immunopathogenesis of the disease: lymphadenopathy, splenomegaly, hepatomegaly, pronounced hepatic lobular architecture, mucosal and visceral ecchymoses, ventral subcutaneous edema, and small vessel thrombosis. Histopathology typically reveals a mononuclear cell infiltrate of periportal regions of the liver as well as of the adrenals, spleen, lymph nodes, meninges, and lungs. Hemosiderophages are typically found in the lymph nodes, liver, spleen, and bone marrow. Immune complex deposition commonly results in glomerulonephritis.

## DIAGNOSIS

The U.S. Department of Agriculture (USDA) has approved three diagnostic tests for detection of EIAV infection, all of which assay for serum antibodies to the p26 core protein of the virus. These include the agar gel immunodiffusion (AGID) test, more commonly known as the *Coggins test*, the competitive enzyme-linked immunosorbent assay (cELISA), and synthetic-antigen ELISA. Most horses seroconvert by AGID within 45 days of infection with EIAV. Other tests that assay for antibody to viral (glyco)proteins include the Western blot and fluorescence polarization, the latter of which is a simple and rapid technique that may gain usefulness as an approved diagnostic test. Another potentially useful diagnostic test, polymerase chain reaction (PCR), is based on detection of viral nucleic acid—either viral RNA (in virions), or proviral DNA (integrated in the host chromosome). This test is very specific but may result in a false-negative result if the primers used to match the “genetic code” of the virus differ from the actual viral genetic sequence. Because isolates have been shown to differ genetically among regions of the country, it is possible that such a test would not detect all isolates.

## TRANSMISSION

Transmission can occur by several means. Vector-borne transmission is most common, with tabanids (horse flies, deer flies) being the primary vectors. The virus does not replicate in the insect. However, virus can remain infectious in the blood that is associated with the tabanid's proboscis for several hours and can be mechanically transferred to another horse. Furthermore, iatrogenic transmission with such

items as blood-contaminated needles, surgical instruments, teeth floats, and nasogastric tubes as mechanical vectors is possible. Risk of transmission to uninfected horses is increased when the source of infected blood is a horse that is undergoing clinical disease. Transplacental, colostrar, lactar, and venereal transmission have also been documented. Foals born to infected dams may acquire antibody to the virus via colostrar transfer. As maternal antibody wanes, the antibody titer to EIAV wanes in uninfected foals, and a qualitative difference in the AGID reaction can be observed over time. Colostrar antibodies are usually undetectable by 6 months of age in noninfected foals born from infected mares. Foals born to mares that are undergoing severe disease manifestations during gestation are more likely to be infected. Inapparent carrier horses, despite appearing clinically normal, can maintain low to moderate levels of replicating virus in the blood and therefore can serve as a reservoir for infection of other horses.

## CONTROL

No treatment or USDA-approved vaccine is currently available for EIAV infection. Therefore control measures, which are largely determined by individual states, are critical to restrict the spread of disease. Most states require that a horse be seronegative within 6 months to a year of entry into the state. Many states also require seronegativity for participation in equestrian events such as shows and races. Despite these requirements, it is estimated that as little as 20% of the equine population is ever tested. As a result, reservoirs of infected horses are maintained, and the actual prevalence of EIAV-infected horses in the United States remains unknown. It is well-established, however, that some regional differences in climate favor the vector and consequently the infection. The states bordering the Gulf of Mexico have the highest incidence of the approximately 2000 seropositive cases reported annually in the United States.

If a horse is seropositive (reactor), an orchestrated series of regulatory events that may vary from one jurisdiction to another occurs. State regulatory officials are contacted first to establish a quarantine of the premises and to promptly retest the reactor. The owner and testing veterinarian are then notified. All horses on the premises are tested; horses that test positive are retested to confirm positivity. Repeated testing at 45- to 60-day intervals under quarantine generally continues until 45 to 60 days after all horses tested are seronegative; the time period is to allow for seroconversion of recently infected horses. Additionally, horses that have had significant exposure to the infected horse(s)—from presence at an equestrian event or at the premises under quarantine—are sought and tested. Reactors may be euthanized, donated to an approved research institution, or maintained in permanent quarantine. Reactors maintained in quarantine must be permanently marked, usually over the right shoulder or neck, with the letter A preceded by the state's USDA identification number and followed by a number assigned to the horse. Reactors are prohibited from interstate travel unless USDA approval is granted for shipment in “sealed containers.”

Control measures for horse farms and ranches should begin with serodiagnostic testing of all horses on the premises, with annual testing of permanent residents. Regions with a

high disease incidence should consider testing all residents biannually. All new horses that will visit or take up residence on the premises should be seronegative within a 3- to 6-month period before arrival. Horses that have negative test results obtained less than 45 to 60 days before arrival may not have had enough time for seroconversion if they were recently infected; these horses should be retested if accepted onto the premises. Fly control should be practiced, and veterinarians and their clients should strictly prevent iatrogenic spread of infection. All equestrian events should require proof of seronegative status; equestrians should encourage organizers of local events to adopt such a policy.

Because a federal eradication program has never been in force for EIA, the persistence of reservoirs of EIAV infected horses must be expected. Owners who face eu-

thanasia or lifetime quarantine of an inapparent carrier of EIAV often find it difficult to understand the threat their horse poses to other horses. They are often equally frustrated by the financial and emotional losses. It is the veterinary community's responsibility to educate horse owners about the disease and its potential consequences so that outbreaks may be limited by rigorous voluntary surveillance testing.

### Supplemental Reading

Sellon DC: Equine infectious anemia. *Vet Clin North Am Equine Pract* 1993; 9(2):321-336.

## CHAPTER 2.5

# Viral Encephalitides

GENEVIEVE FONTAINE-RODGERS  
*Gainesville, Florida*

**A**rboviruses or arthropod-borne viruses, including Togaviridae and Flaviviridae, may cause encephalitis or myeloencephalitis in horses. Despite similarities in transmission cycle and clinical presentation of the disease they cause, these viruses differ in antigenicity and geographic distribution.

### ALPHAVIRUS ENCEPHALITIDES

Eastern, western, and Venezuelan equine encephalitis (EEE, WEE, and VEE, respectively) viruses are endemic in the Americas and occasionally cause epidemics of encephalitis in horses and humans. These alphaviruses are members of the family Togaviridae and are closely related but antigenically distinct. Alphaviruses are small, single-stranded positive sense RNA viruses. The 12-kilobase pairs genome is enclosed in a 40-nm-diameter nucleocapsid composed of multiple copies of the capsid (C) protein. Virions are enveloped in a membrane acquired through budding out of the host's cell and modified by the insertion of heterodimers of two glycoproteins (E1 and E2) that carry multiple antigenic sites.

### Epidemiology

#### Eastern Equine Encephalitis

In North America, EEE virus is perpetuated in a cycle that involves a mosquito, *Culiseta melanura*, as the primary or enzootic vector and passerine birds as the amplifying hosts. Because *C. melanura* is mostly ornithophilic, transmission of EEE in horses or people necessitates the intervention of mosquito species that feed on birds as well as

other animals, such as *Coquillettidia perturbans* or members of the *Aedes* genus. Altogether, EEE virus has been isolated from 23 different mosquito species. Epidemics of EEE usually occur within close proximity of deciduous wetlands where *Culiseta* organisms abound. Climactic events associated with epidemics of EEE include excessive rainfall and higher-than-normal water temperatures that hasten development of the summer generation of the primary vector.

Geographic distribution of EEE extends from Canada to essentially all of the United States east of the Mississippi River, a number of western states, the Caribbean, and Central and South America. Because *C. melanura* is found in temperate regions, EEE is not endemic in southern Florida or the Caribbean. However, sporadic introduction of EEE virus by viremic birds during migration may be responsible for the cases reported in these areas. In the United States the infection is most commonly documented in the southeastern states. EEE virus is divided into North and South American antigenic variants based on hemagglutination inhibition tests. Nucleotide sequencing and phylogenetic analyses further divide the South American variant into 5 different lineages. In addition to their genetic differences, North and South American variants differ by their cycles. The South American virus uses a mosquito of the *Culex* subgenus as primary vector and small rodents as reservoirs. In the Northern part of the virus range, equine and human cases occur between July and October, but cases are observed year-round in Florida. The South American variant rarely causes disease in humans and is infrequently associated with epidemics of EEE in horses. It is widely accepted that humans and horses are dead-end hosts for EEE because the viremia is insufficient to perpetuate the cycle.



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### ***Western Equine Encephalitis***

In the western United States, WEE virus is maintained in a cycle among birds and *Culex tarsalis*, the principal mosquito vector of WEE that breeds mainly in waste irrigation water in farmland and pastures. In most years, transmission from this enzootic cycle results in a low level of endemic infection in the human population; at intervals of 5 to 10 years, however, viral transmission in the maintenance cycle is more intense, and humans and horses become infected at epidemic and epizootic levels. In 1941 the largest and most extensive WEE outbreak on record was reported from the northern plains states and neighboring Canadian provinces. As many as 300,000 cases in horses and 3400 in humans were reported. More recently in 1975, an outbreak in the Red River Valley was reported and caused disease among humans and horses in North Dakota and Minnesota. Cases of encephalitis diagnosed as WEE in horses located west of the Mississippi are in fact due to Highlands J virus, an alphavirus that belongs to the WEE family. Affected humans and horses do not develop a sufficient viremia to participate in the life cycle of WEE virus and are therefore dead-end hosts.

### ***Venezuelan Equine Encephalitis***

VEE viruses undergo two distinct transmission cycles: (1) enzootic, which is associated with stable sylvatic foci, involves rodents, and causes sporadic human outbreaks but little disease in equids and (2) epizootic, which is observed in a wide range of ecologic settings, is associated with many different vertebrates, and causes high morbidity and mortality among equids and humans. A number of antigenically different subtypes of VEE viruses have been identified. Variants belonging to the subtype I—varieties A/B and C—are responsible for epidemics/epizootics. In 1993 and 1996, however, the endemic variant IE was also associated with disease and death in equids. Comparison of nucleotide sequences suggests that epidemic viruses emerge from endemic virus cycles. From 1936 to 1968, equids in several South American countries suffered devastating outbreaks. In 1969 the disease moved north throughout Central America, finally reaching Mexico and Texas in 1971. A more recent outbreak that began in northwestern Venezuela in April of 1995 spread westward to Colombia.

Enzootic subtypes of VEE are endemic to South and Central America and are sporadically identified in Florida and Colorado. These subtypes generally do not spread to other localities. Epizootic subtypes, on the other hand, can spread rapidly through large populations. Although rodents and other small animals are the most important amplifiers in endemic preservation of the virus in tropical forests, swamps, and marshlands, equids are the most important amplifier hosts in large epidemic outbreaks because they develop an important viremia. Although other animals—such as cattle, swine, and dogs—can become infected, they generally do not show signs of the disease or contribute to its spread. Humans and horses are infected by a wide variety of mosquito vectors, including *Culex*, *Mansonia*, *Psorophora*, and *Aedes* species. Humans acquire infection as an incidental dead-end infection of the normal animal-mosquito-animal cycle in nature.

## **Clinical Signs**

In affected horses, alphavirus encephalitides elicits a wide array of clinical presentations that range from lack of signs to clinical signs that reflect brain or spinal cord dysfunction. The infection generally begins with an incubation period of several days, during which a biphasic viremia takes place. During the viremic period, horses usually exhibit nonspecific signs such as fever, lethargy, and stiffness. Horses then may progress to exhibit clinical signs of neurologic disease, the severity of which varies according to the virus involved and the extent of the lesions in the central nervous system (CNS). Cerebral lesions often result in behavior changes, such as excitability, aggressiveness, hyperesthesia, or profound lethargy. Other signs of dementia often observed include continuous chewing movements, circling, compulsive walking, head-pressing, or leaning against a wall.

Cerebral and spinal cord involvement may result in the following clinical signs: blindness, signs of cranial nerve deficits (facial, lingual, and pharyngeal paralysis), hypermetria, ataxia, and proprioceptive deficits or paresis of the trunk and limbs. Death is generally preceded by a period of recumbency, during which horses may become comatose or experience seizure activity. Horses that recover do so over a period of weeks to months and may have residual neurologic deficits. Mortality rates for EEE range from 75% to 95%, and complete recoveries are rare. WEE has a lower mortality rate (19% to 50%), and horses that recover have fewer neurologic deficits than with EEE or VEE, which carry a mortality rate ranging from 40% to 80%. VEE is often accompanied by a sustained fever, and affected horses may present ulcers of the oral mucosa, diarrhea, pulmonary hemorrhage, and abortion. Horses affected with WEE rarely progress beyond the transient febrile phase associated with the viremia. On the other hand, horses with EEE generally exhibit signs of cerebral dysfunction within a few days after infection.

## **Diagnosis**

In the case of an outbreak, establishing a definitive diagnosis is important to implement appropriate control measures. Although clinical signs and epidemiologic features may suggest equine encephalomyelitis due to an alphavirus, a specific diagnosis is made based on viral isolation or identification of viral nucleic acid by reverse transcriptase-polymerase chain reaction (RT-PCR) or by the presence of antibodies to a specific virus. EEE, WEE, and VEE viruses may be isolated from brain tissue of infected horses via Vero-cell culture or mouse inoculation. Attempts to detect viruses in serum samples are usually unsuccessful, unless the sample is collected during the incubation period, when a more significant viremia is likely to be present. RT-PCR offers a sensitive and specific test by detection of viral nucleic acid in CNS tissue or cerebrospinal fluid (CSF). Hemagglutination-inhibition (HI), complement fixation (CF), serum neutralization (SN), mouse inoculation, and antibody-capture enzyme-linked immunosorbent assay (ELISA) are used to detect antibodies.

Serologic diagnosis of EEE, WEE, or VEE may be complicated by the presence of vaccinal or colostral antibodies. In newborn foals, antibody titers closely reflect

colostral titers and rapidly decline. In the case of EEE the half-life of serum antibodies is 33 days. Although elevated titers in single serum samples suggest the presence of an infection, a fourfold rise in paired samples is diagnostic. In cases in which the initial sample is collected during the peak viremia, a rise may not be observed and the subsequent sample may reveal a lower titer. Horses with EEE usually do not live long enough to obtain paired samples. Using the ratio between EEE and WEE titers to diagnose EEE is an insensitive as well as nonspecific method and should not confirm a diagnosis. On the other hand, high immunoglobulin M (IgM) titers suggest recent exposure to EEE virus and may be detected with an antibody-capture ELISA.

### Pathology

Analysis of the CSF often reveals an increased cellularity (50 to 400 cells per  $\mu$ l), with a high percentage of neutrophils, and an elevated protein concentration (more than 100 mg/dl). These changes are more prominent with EEE than WEE or VEE.

### Prevention

Reducing exposure to vectors may help prevent arboviral diseases. Preventive measures include eliminating mosquito-breeding sites, such as stagnant water and decaying vegetation; stalling horses; applying insect repellent at dusk and dawn when mosquitoes bite; screening stalls; and using fans. Local mosquito-control agencies may use aerial and ground-based spraying of adulticide products in areas where significant viral activity is detected by surveillance of mosquito pools or sentinel flocks or reports of human and/or veterinary cases of encephalitis.

Killed virus vaccines against alphaviruses are available for horses and should be used as part of the routine protocols. Recommendations vary according to the location of the animal. In Northern regions where the mosquito season is limited to the warm months, horses should be vaccinated against EEE and WEE once a year before the vector season. In the southeastern states, vaccination against EEE and WEE is recommended up to 4 times a year because of the prolonged vector season. In areas bordering Central America or for horses traveling to endemic areas, vaccination twice a year against VEE is recommended. Foals from vaccinated mares are generally protected for 6 to 7 months. Vaccination of foals against EEE should be started at 4 months of age in endemic areas and repeated at 6 months and 1 year of age.

## FLAVIVIRUS ENCEPHALITIDES

### West Nile Virus Encephalitis

#### Epidemiology

West Nile virus (WNV) is a flavivirus that belongs to the Japanese encephalitis virus antigenic complex that also includes St. Louis encephalitis virus. In August 1999, WNV was identified as the causative agent of encephalitis in birds, horses, and humans in New York City and Suffolk County, N.Y. Since then, WNV activity has spread north-

ward and southward along the U.S. East Coast and westward to several states. The geographic spread of WNV may be due in part to migration of avian reservoir hosts; pronounced northward spread of the virus was noted in late spring and early summer, whereas southward spread was observed in the late summer and early fall.

Before its introduction into the United States in 1999, which signaled its first occurrence in the Western Hemisphere, WNV was endemic in Europe, Africa, west and central Asia, Oceania, and the Middle East. Cases of equine encephalomyelitis were reported in France, Italy, Portugal, Morocco, Egypt, and Israel. The strain identified in the U.S. Northeast in 1999 is closely related to a strain of WNV isolated from a goose in Israel in 1998, but how the virus was introduced in America will most likely remain unknown. Increased intercontinental travel and connections are likely to increase the spread of pathogens such as WNV to new areas, where they may encounter naïve populations of susceptible hosts. The virus cycles between competent bird reservoir hosts that sustain an infectious viremia for 1 to 4 days subsequent to exposure—after which these hosts develop lifelong immunity—and mosquitoes that carry the virus in their salivary glands. Susceptible birds may become ill or die of myeloencephalitis. Humans, horses, and other mammals are considered dead-end or incidental hosts; no evidence suggests that they develop a sufficient viremia to complete the cycle. Serosurveys that are performed in areas with documented viral activity reveal that numerous species such as cattle, camels, dogs, and cats develop immune responses to the virus without becoming ill, except for rare cases reported in the canine and feline species.

#### Clinical Signs

Serosurveys conducted in 1999 suggest that not all horses exposed to WNV develop neurologic disease. In horses with clinical signs of myeloencephalitis, ataxia is the most common feature, and rear limb involvement is observed more often. Affected horses also commonly display muscle fasciculations or tremors—in particular, around the nose and lips. Some horses exhibit transient hypersensitivity that is characterized by excessive reactions to touch or sound. In 1999 and 2000, fever was documented in approximately one third of the infected horses.

The onset of clinical signs is generally acute, and in most cases, improvement is noticed within days. Euthanasia is generally warranted in the most severely affected horses that are unable to stand because of hind limb paralysis or when signs of cerebral lesions (such as seizures or coma) are present. In 1999 and 2000, approximately 35% of the horses with neurologic disease either died or were euthanatized 3 to 4 days after the onset of clinical signs, whereas the other cases resolved completely over several weeks to months. During the 1999 and 2000 outbreaks, equine cases were observed between mid-August and late-October, following the identification of wild bird and human cases, but in 2001, cases were confirmed from June to December and beyond in Florida. These data suggest that cases might be observed year-round in areas with prolonged vector seasons. No significant age, gender, or breed predisposition was detected among affected horses, and the outcome was not influenced by any of these categories.

### **Diagnosis**

WNV encephalomyelitis should be suspected when neurologic disease is observed in a horse that lives in an area where WNV activity is documented. Laboratory testing may be performed on serum, whole blood, CSF, or brain tissue. HI is used as a screening test on serum. Titers above 1:10 suggest a suspect case, but cross-reactivity between antibodies to WNV and other antigens affect the specificity of this test. Confirmation of a positive case of WNV encephalitis currently relies on IgM-capture enzyme-linked immunosorbent assay (MAC-ELISA) of serum or CSF, plaque reduction neutralization test (PRNT) of serum, and viral isolation and PCR performed on brain tissue. A MAC-ELISA revealing serum IgM titers greater than or equal to 1:400 suggests recent exposure to the virus, whereas PRNT with titers greater than or equal to 1:10 indicates an IgG response. High IgM titers decline within less than 2 months after exposure, whereas elevated IgG titers may not be present in the acute phase of the disease but may persist at least 15 months.

Vaccination does not interfere with the ability to diagnose acute cases because no IgM are detectable in vaccinated horses. According to the Animal and Plant Health Inspection Service (APHIS), Veterinary Services, a confirmed equine case of WNV encephalitis has neurologic signs and any of the following: viral isolation from blood, CSF or tissue; fourfold increase in IgG detected by PRNT on appropriately timed paired sera; or detection of high-IgM antibodies and IgG greater than or equal to 1:10 by PRNT in a single serum sample. Cytologic examination of the CSF presents a wide variety of changes in cell count and protein concentration.

### **Prevention**

Because WNV is an arbovirus, measures to avoid vectors similar to the ones recommended for alphavirus prevention should be implemented. A killed vaccine was developed to aid in the prevention of WNV encephalitis in horses. Currently the vaccine is released under conditional license because data regarding its efficacy are not yet available. Current recommendations are initial vaccination followed by a booster 3 weeks later and annually thereafter. These recommendations may be reviewed when research results become available.

## **Japanese Encephalitis**

### **Epidemiology**

Japanese encephalitis (JE) virus is a flavivirus that affects horses and humans. Originally documented in East Asia, this virus has spread westward to Pakistan and eastward to the north of Australia. Outbreaks occur in areas where the virus encounters immunologically naïve populations of susceptible hosts. In endemic areas the cycle involves mosquitoes of the *Culex* genus, pigs, or ardeid birds such as herons or egrets. Horses and humans do not generate enough viral amplification to contribute to the viral transmission, although experimental horse-to-horse transmission has been documented. Disease in humans and horses occurs year-round in tropical areas and generally at the

end of the summer in temperate regions. Over the last three decades, geographic distribution of JE has significantly expanded, perhaps because of the establishment of large pig farms and because of deforestation, which favors the expansion of mosquito habitats.

### **Clinical Signs**

From outbreaks in racehorses in Malaysia and Singapore, three main clinical syndromes have been identified. The transient type is characterized by fever, anorexia, decreased activity, and congested or jaundiced membranes for a period of 2 to 3 days. In the lethargic type, fever, jaundice and petechiae, incoordination, dysphagia, impaired vision, neck rigidity, and radial paralysis last for approximately 36 hours, with complete recovery in 4 to 5 days. Horses with the hyperexcitable type have fever, demented behavior, profuse sweating, teeth grinding, spasmodic muscle twitching, ataxia, recumbency, and death. The latter syndrome was observed in less than 5% of the cases. Mortality rate ranges from 5% to 40%, depending on the outbreak. Recovery is associated with residual deficits in some cases.

### **Diagnosis**

Brain lesions are not characteristic for JE and reflect a diffuse nonsuppurative encephalomyelitis. JE should be suspected if clinical signs of neurologic disease and fever are observed in horses in an endemic region. Confirmation of the diagnosis relies on serology; viral isolation; or detection of viral nucleic acid in CSF, tissue, or blood. Because serology for JE lacks specificity, the panel of tests used varies according to the geographic area, depending on which other flaviviruses are known to be present. A fourfold rise in antibodies between acute and convalescent serum collected 2 to 4 weeks apart is considered diagnostic.

### **Prevention**

Vector control and prevention are recommended. Control of an outbreak also involves restriction of movement of amplifying hosts. Vaccination of horses with an inactivated product has reduced the incidence of JE in regions where it has been implemented. Primary immunization consists of two injections 4 weeks apart and is followed by annual boosters before the peak of the vector season. Foals from vaccinated mares are generally protected for 4 to 5 months, after which a standard vaccination protocol should be started.

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## CHAPTER 2.6

# Vesicular Stomatitis

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**V**esicular stomatitis (VS) is a viral disease of horses, cattle, and other livestock and is reported to occur exclusively in the Western Hemisphere. The disease is characterized by the appearance of vesicles, ulcers, and erosions located especially on the tongue, oral and nasal mucosa, and coronary bands.

VS is caused by infection with either of two serotypes of vesicular stomatitis virus (VSV): Indiana (VSV-Indiana) or New Jersey (VSV-New Jersey). These RNA viruses are in the *Vesiculovirus* genus of the family Rhabdoviridae. Other vesiculoviruses and VSV-subtypes (e.g., Cocal, Alagoas, Chandipura, Piry, Isfahan, Chalcaqui) have been reported to cause disease in humans and animals in South America, India, and Iran.

VSV can cause disease in horses and other equids, cattle, swine, and llamas. Horses may be more susceptible than are cattle to infection with VSV, development of clinical signs of VS, or both. VS is a zoonotic disease and can cause a flulike disease in people working closely with infected animals. Serologic evidence of exposure has been reported in many other species, including cotton rats, coyotes, deer, deer mice, ducks, dogs, donkeys, elk, goats, pronghorn antelope, raccoons, turkeys, and wood rats.

The prevalence rates in horses, as indicated by either serologic evidence or the presence of clinical disease, vary greatly among individual premises during outbreaks. Disease may be apparent in animals on one premises, but animals on adjacent premises may remain unaffected. The infection rate (determined serologically) is often 80% to 100%; however, generally only 30% of infected animals on a farm show clinical signs. A higher prevalence of clinical disease appears in horses housed on pasture, which may be due to higher rates of exposure and infection or may be a result of other pasture-associated factors that either increase the pathogenicity of the virus (e.g., more effective mode of virus transmission) or the susceptibility of the horses (e.g., increased rate of mucosal abrasions). Individual animal factors clearly contribute to susceptibility to infection and development of clinical disease, as horses managed identically do not necessarily have the same rates of disease. For example, horses less than 1 year of age are less likely to develop clinical signs of VS, although infection and seroconversion still occur.

VS has been reported only in the Western Hemisphere. Infections occur seasonally every year in tropical areas of Southern Mexico and Central and South America and occur sporadically or as outbreaks in temperate areas of North and South America. Seasonality is also seen in temperate areas, with outbreaks occurring primarily from early summer to late fall. During recent VS outbreaks in the

United States (in 1995, 1997, and 1998), animals in Arizona, Colorado, New Mexico, Texas, Utah, and Wyoming were affected. Before 1995, no cases of VS had been reported in the United States since 1985.

### PATHOGENESIS

The complete epidemiologic cycle of VSV has not been elucidated but is believed to include both an indirect and direct means of virus transmission. Epidemiologic data, including limitation of the disease to specific seasons and distinct ecologic zones, suggest arthropod-borne transmission of VSV. The lack of identification of a naturally occurring viremic host species that could act as a reservoir for hematophagous insect spread and the disparity among anatomic areas commonly attacked by biting insects and those commonly affected by clinical VS lesions complicates this hypothesis.

The virus is transmitted directly to susceptible hosts by contact with active lesions, saliva of animals with oral lesions, and contaminated fomites such as watering tanks. Abrasions of skin or mucous membranes may facilitate transmission of the virus and subsequent lesion formation. VSV has been isolated from nonhematophagous arthropods such as *Musca domestica*, which may play a role in mechanical transmission of the virus.

Once VSV gains access to the animal host, virus multiplication is thought to remain localized in the epithelium. The virus has not been detected in the blood of naturally infected animals. After exposure, vesicles tend to appear in approximately 1 to 3 days. In each affected animal, lesions are generally restricted to one anatomic region, and new lesions do not typically develop more than 3 to 4 days after the first ones appear. Lesions typically have resolved in approximately 10 to 14 days. Virus is present in high concentrations in vesicles and is shed from active lesions. Virus shedding has ceased by 6 to 7 days after exposure. No evidence suggests that infective VSV is shed after lesions have begun to heal. Virus is not shed in urine, feces, or milk.

### REGULATORY ISSUES

Clinically, VS is indistinguishable from foot and mouth disease (FMD) and is therefore a critical consideration in FMD control programs in the United States and worldwide. Likely because of this similarity, VS has been classified by the Office International des Epizooties (OIE) as a "List A" disease, along with FMD and other serious and/or economically important diseases; thus VS is now subject to stringent regulations when it occurs in any species (although

FMD does not occur in equids). When VS is confirmed in the United States, nonaffected states and most foreign countries initiate strict transport embargoes, and movement of livestock is hindered by increased regulatory surveillance and quarantines of affected premises. These events have a major economic impact on the equine industry at every level.

To comply with international regulations, the United States requires veterinarians to identify animals—including horses—with clinical signs of VS (vesicles or ulcers in the mouth or nose or on the coronary bands, mammary glands, or external genitalia) and to notify the state veterinarian or USDA:APHIS:Veterinary Services immediately. These animals then must be inspected by a veterinarian from the USDA:APHIS:Veterinary Services. At this time a blood sample and swab of the lesion are collected from each suspect animal, and all premises with suspect animals are immediately quarantined pending laboratory confirmation of the disease (generally 48 hours). Premises that have confirmed VS-positive animals remain quarantined for 30 days after clinical signs have been cleared from all animals on the premises, as determined by either a federal, state, or accredited private veterinarian.

## CLINICAL SIGNS

The classic clinical sign of VS is the appearance of vesicular lesions on the mucous membranes and/or coronary bands of infected animals. Most commonly affected are the oral and nasal mucosa, tongue, and lips. Lesions may also appear on the mammary glands or external genitalia, and some owners have reported lesions on the ears and face. The clinical signs associated with VS are extremely variable. As previously mentioned, up to 70% of infected animals may not demonstrate overt signs of disease, and some infected animals may show only a few days of mild depression.

Initially, blanched areas appear that subsequently develop into vesicular lesions. Animals are generally febrile during this vesicular phase. Typically, the vesicular lesions and fever are not observed in the index case(s), and the first examination occurs when more obvious signs appear (e.g., ulcerative, erosive, and/or crusting lesions, a swollen muzzle and lips, lameness, salivation, and/or reluctance to eat). Mucosal necrosis and sloughing (especially of the dorsum of the tongue) may be extensive. Lesions generally have resolved completely in 10 to 14 days.

VSV is considered nonlethal. Deaths that do occur are generally due to secondary complications, such as bacterial infection of the lesions, mastitis, and cachexia and/or dehydration secondary to reluctance to eat or drink. Chronic hoof wall deformities secondary to coronary band lesions may occur. Complications are rarely severe enough to warrant euthanasia.

## DIAGNOSIS

Lesions are generally not detected until the vesicular phase has passed; therefore differentiation among etiologies of ulcerative and erosive lesions is required for definitive diagnosis. Trauma of the oral and nasal cavities and coronary bands due to any cause is the primary differential for VS in horses. Sunburn—with or without predisposing systemic photosensitization—is also commonly confused with VS.

Edema, vesiculation, crusting, and erosion associated with sunburn of the nonpigmented skin, especially in the lightly haired areas of the face and lower limbs, commonly occurs in the summer months in high-altitude areas of the southwest United States. Systemic photosensitization may predispose animals to sunburn and is associated with certain medications, ingested plants, and liver disorders.

Very few infectious agents other than VSV and other vesiculoviruses have been definitively associated with vesicle formation in horses. In some cases, infections with equine arteritis virus (EAV), Jamestown Canyon virus, caliciviruses, and equine herpesviruses may be associated with oral ulcers and erosions. Use of wood shavings of the Simaroubaceae family, which contain the compounds quassin or neoquassin, as bedding material can cause apparent outbreaks of ulcerative stomatitis in groups of horses. Physical trauma induced by coarse forage or plant awns, including triticale hay, also can cause multiple horses in a group to develop oral ulcers, thus mimicking an outbreak of an infectious disease.

Cantharidin is the toxin contained in blister beetles (*Epicauta* spp.), which may be present in baled alfalfa hay. Ingestion of the beetles can cause vesicular or ulcerative lesions as well as severe systemic signs. Adverse reactions to the administration of pharmaceuticals or over-the-counter medications, including nonsteroidal antiinflammatory drugs (NSAIDs), may cause ulceration or erosion of the oral mucosa, generally in combination with systemic manifestations. Pemphigus foliaceus, equine exfoliative eosinophilic dermatitis and stomatitis, squamous cell carcinomas, and melanomas can in some cases mimic the clinical picture of VS. Recently, several apparent outbreaks of ulcerative stomatitis were reported in horses in the United States and New Zealand. Extensive investigations failed to determine any infectious or other cause for these outbreaks. The most significant differential diagnosis for VS in nonequine species is FMD, which does not occur in horses.

## LABORATORY DIAGNOSIS

As previously mentioned, the clinical signs associated with VS are extremely variable, and diagnosis cannot (and should not) be made on the basis of clinical signs alone, especially at the outset of an outbreak on a premises. Definitive diagnosis of VSV infection must be laboratory-based.

Serologic tests are available for detection of serum antibodies to VS viruses. Typically, a competitive enzyme-linked immunosorbent assay (cELISA) is used as a screening test. This test is rapid and detects both immunoglobulin M (IgM) and immunoglobulin G (IgG). Serum neutralization (SN) and complement fixation (CF) tests are also used. These three tests are serotype-specific, and little cross-reactivity between antibody to VSV-New Jersey and VSV-Indiana occurs. Antibody can be detected within 5 to 8 days after infection. Both the cELISA and SN tests detect serum IgG that may be present in the serum for 1 to 3 years, thus making the interpretation of titers in a single serum sample difficult. An elevated CF titer in a single serum sample is more diagnostic of recent infection, as CF titers tend to become undetectable by 110 days after infection, but high concentrations of IgG may affect the CF test. A rising SN or CF titer therefore is required to definitively diagnose recent VSV

infections; however, considerable variability of antibody responses exists among individual infected animals. Some laboratories use an ELISA test to specifically detect serum IgM and therefore improve the ability to differentiate active VS infections from past exposure; however, this test is currently being used only in a research capacity.

Virus isolation may be used to detect live virus in epithelial tags, swabs, and/or biopsies from active lesions. Virus isolation is unrewarding once lesions have begun to resolve. As the virus does not spread hematogenously, virus cannot be isolated from whole blood. Histopathology of biopsy samples is generally not used to diagnose VS, as observed changes are not sufficiently specific. However, biopsies may be useful in diagnosing lesions associated with grass awns when plant material is seen, especially if serologic testing is negative for VSV.

A polymerase chain reaction (PCR) assay has been developed as a research tool to detect viral RNA in biologic samples and is currently undergoing validation for use on field samples. The testing technique is potentially more sensitive than virus isolation, as PCR detects only RNA and does not require the presence of active virus.

## TREATMENT

VS is typically a self-limiting disease with a short convalescent period. In most cases, no specific treatment is indicated, and horses recover uneventfully within 2 weeks. Even in severe cases, only supportive care and prevention of secondary complications is required until lesions resolve. It should be stressed that VS is considered a zoonotic disease and that animal healthcare providers and owners who treat and handle horses with active lesions may become infected. Therefore sound biosecurity practices, such as the wearing of disposable protective gloves, frequent hand-washing, and avoidance of contact with infected saliva, are recommended.

Secondary bacterial infections of the lesions can be minimized by frequent cleaning with commonly used mild antiseptics (such as Nolvasan) or application of topical antibiotics. Cachexia can be prevented or remedied with the provision of palatable feeds that are easily masticated, such as complete feed pellets softened with water. Providing fluids and/or feed via a stomach tube might become necessary in horses that are severely anorexic. Rarely, dehydration becomes severe enough to require intravenous (IV) fluid support. Corrective shoeing might be required if the hoof wall deformities secondary to coronary band lesions become sufficiently severe to interfere with normal function.

## PREVENTION AND CONTROL

Implementation of specific management practices can reduce the risk of spread of VS among and within premises. During regional outbreaks, all new arrivals (equine, bovine, ovine, and porcine) at a premises should be considered suspect and quarantined for 3 to 5 days. Even minimal contact with outside livestock should be avoided. Clinically affected animals should be isolated from unexposed animals. During outbreaks, all at-risk animals should be examined daily for oral lesions.

Equipment—including feeders, waterers, salt blocks,

brushes, and tack—should not be shared between affected (or suspect) and unaffected animals, and equipment and areas should be disinfected before noninfected animals are introduced. Furthermore, all personnel should change or disinfect clothes and boots and wash their hands after working with infected animals. The viruses are easily inactivated with 1% formalin, 10% sodium hypochlorite (bleach), and other commonly used disinfectants. They are also inactivated by exposure to 58° C for 30 minutes; however, they can survive in the environment in soil at temperatures from 4° to 6° C. Because all modes of transmission have not been elucidated, contact between infected animals and poultry, dogs, cats, and nonessential personnel should be minimized.

Although insect transmission of VSV has not been proven, insect contact with livestock should be minimized; horses should be stabled during periods of increased insect activity; and insect repellents should be applied frequently on horses. Insects should be controlled in areas where horses are housed, and animals should be moved from pastures containing waterways during the summer months to help control disease spread.

No vaccines are commercially available to prevent VSV infections in animals in the United States or Mexico, although during several outbreak years (including 1963, 1985, and 1995) autogenous killed virus vaccine was approved for use in horses and cattle on a limited basis in the southwestern United States. Several vaccines are being developed or evaluated experimentally in areas of Central and South America, and a commercial VSV vaccine is in use in Colombia. However, even horses with high levels of circulating antibody from natural exposure have been shown to be susceptible to experimental challenge with homologous virus, potentially due to epithelial localization of infections, which could diminish the protective effect provided by antibodies circulating in the serum. Therefore the effectiveness of any parenterally administered vaccine is questionable. Moreover, because of the potential international regulatory consequences of animals developing serum antibody titers against VSV, research is being conducted to develop a DNA vaccine that would elicit production of antibody that could be differentiated from that elicited through natural exposure.

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## CHAPTER 2.7

# Lyme Disease

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Lyme disease is caused by the spirochete *Borrelia burgdorferi*, an organism that is maintained in a 2-year enzootic cycle that involves *Ixodes* spp. ticks and mammals (Figure 2.7-1). The deer and the white-footed mouse (*Peromyscus leucopus*) are the most common mammals involved in maintaining the life cycle. Infection in mammals generally occurs from larval or nymph bites in the spring and summer or adult (female) tick feeding in summer, fall, or winter. In horses, it is not known whether larval and nymph bites play an important role in Lyme infection. In most instances, the ticks must be attached to the mammal for at least 24 hours for *B. burgdorferi* transmission. A large percentage of adult horses in the more eastern parts of the Northeast and Mid-Atlantic states are or have been infected with *B. burgdorferi*. This fact is well-documented by serologic surveys, which demonstrate that up to 75% of adult horses in some of these areas are seropositive. Seroprevalence in other parts of the United States has not been reported but would be expected to fluctuate in a manner similar to that of the human disease.

### CLINICAL SIGNS

A broad spectrum of clinical signs has been attributed to *Borrelia* infection in horses, but cause and effect have been difficult to document. Clinical signs most commonly attributed to equine Lyme disease include low-grade fever, stiffness and lameness in more than one limb, muscle tenderness, hyperesthesia, swollen joints, lethargy, and behavioral changes. Neurologic dysfunction and panuveitis have been reported in a horse and a pony. Fever and limb edema commonly reported in association with recent *Borrelia* infection (proven by seroconversion) are most often the result of *Anaplasma phagocytophila* infection, as many ticks are dually infected with both *Borrelia* and *A. phagocytophila*.

In one report, *Borrelia* infection (confirmed by serology and/or spirochetemia) was more common in horses with lameness and/or behavioral changes than in horses in the same region without these clinical signs. Experimental infection in ponies causes disease in the skin, muscle, peripheral nerves, and both perisynovial nerves and blood vessels, but clinical signs are not obvious.

### DIAGNOSIS

The diagnosis of Lyme disease is based on the housing in an endemic area, compatible clinical signs, ruling out of other causes for these signs, and finding of a high (generally >300 KELA units) enzyme-linked immunosorbent as-

say (ELISA) titer or a positive Western blot (WB) for *B. burgdorferi*. If the ELISA titer is greater than 300, the probability that the WB will be positive is 99%. The WB is most useful in those cases with moderate ELISA titers (200-300) or in cases in which the horse may have received the commercially available canine vaccine.

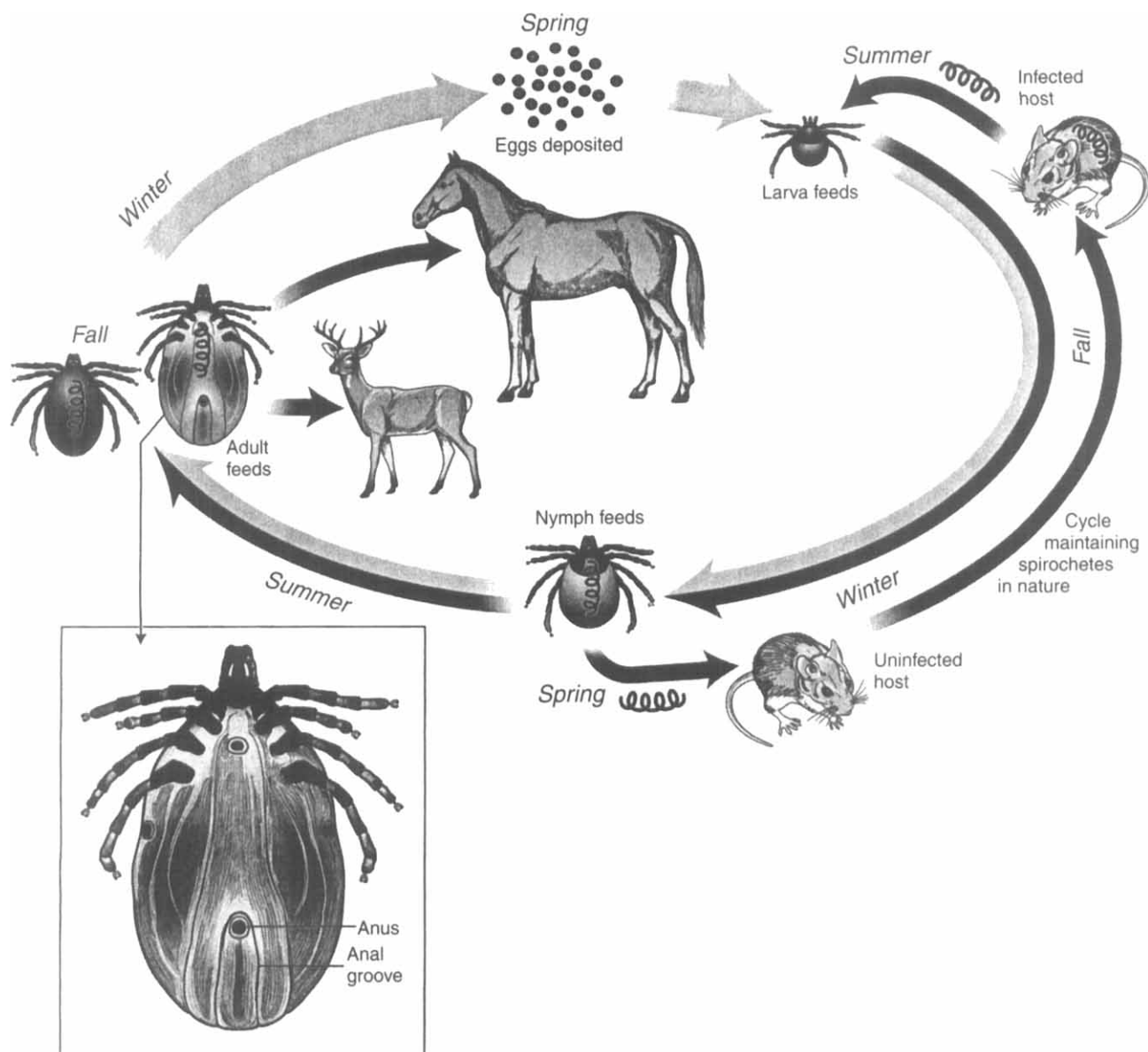
Time from infection to seroconversion appears to be 3 to 10 weeks. The major limitation of serologic tests is that they do not distinguish between active infection and sub-clinical exposure. For this reason, tests that directly detect the spirochete are being developed. Detection of *B. burgdorferi* DNA in a synovial membrane of a painful joint by polymerase chain reaction (PCR) would indicate active infection. The sensitivity of PCR amplification of a synovial membrane biopsy in the horse is currently unknown.

Common disorders that may be confused with Lyme disease and should be ruled out include hock osteoarthritis, osteochondrosis, polysaccharide storage myopathy, chronic intermittent rhabdomyolysis, thoracic spinous process osteoarthritis, and equine protozoal myelitis. Diagnostic tests that may be useful in ruling out these diseases include thorough lameness and neurologic examinations, radiographs, scintigraphy, muscle biopsy, cerebrospinal fluid (CSF) collection and appropriate testing, and serum concentrations of muscle enzymes (before and after exercise).

### TREATMENT

The two most commonly used drugs in the treatment of Lyme disease in horses are intravenous (IV) tetracycline and oral doxycycline. Tetracycline has been used most commonly for acute cases with stiffness, limb edema, and fever. Although these animals generally seroconvert to *B. burgdorferi* after treatment, the clinical signs are possibly or likely a result of *A. phagocytophila* rather than *B. burgdorferi*. Horses with what are believed to be more typical signs of Lyme disease (i.e., chronic stiffness, lameness, and hyperesthesia) are most frequently treated with doxycycline (10 mg/kg PO q12h). Duration of treatment is often 1 month, but the rationale for this duration is only empirical. Horses treated with doxycycline should be observed for changes in stool consistency, as diarrhea will occur in a low percentage of treated horses. Tetracycline (6.6 mg/kg IV q24h) given for 1 week before doxycycline treatment is begun may provide a more rapid clinical response. Cefotiofur (2-4 mg/kg IV or IM q12h) has also been used to treat equine Lyme disease. A decline in antibody concentration often occurs with the previously listed treatments, but it does not mean that the organism is eradicated from





**Figure 2.7-1** A 2-year enzootic cycle of *Borrelia burgdorferi* and distinguishing features of *Ixodes* species ticks. Female ventral abdomen (insert).

the body. Recurrence of clinical signs is often reported after treatment is discontinued.

Other treatments that can be considered supportive include chondroprotective agents, nonsteroidal antiinflammatory drugs (NSAIDs), and acupuncture. Acupuncture may be especially valuable for hyperesthesia/perineuritis syndromes that often show little response to NSAIDs.

## PREVENTION

Prevention of Lyme disease in endemic areas could involve the prevention of tick exposure or prolonged (>24 hr) attachment and the provision of early antimicrobial treatment after *Ixodes* exposure or vaccination. Various insecticidal sprays can be used to prevent tick infection, but most are not approved for use in horses, as efficacy in the horse is unproved. Currently, no adverse effects are known to result from use of the more common canine tick sprays (e.g.,

Fipronil [FrontLine]) in the horse. Spraying is most commonly used when adult ticks are noticeable in late summer, fall, or early winter, but infections with larval/nymph stages earlier in the year should also be considered. If ticks are found on the horse, they should be identified to determine whether they are *Ixodes* spp. (see Figure 2.7-1), the only species of North American tick known to transmit *B. burgdorferi*. Ponies have been protected by vaccination against experimentally induced *B. burgdorferi* infection, but an equine-approved vaccine is not commercially available at this time. Value of the canine vaccine in the horse is unknown.

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## CHAPTER 2.8

# Salmonellosis

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**S**almonella infection is one of the most important causes of enteric disease in horses, both in terms of morbidity and mortality. Infection in foals commonly results in both intestinal and extraintestinal disease, the latter of which is associated with a high mortality. The organism is difficult to manage in that it is omnipresent, environmentally resistant, and greatly amplified by symptomatic animals. The economic impact of salmonellae is not only attributed to the direct costs associated with treatment and the value of animals that fail to survive, but also through widespread contamination of equine boarding facilities and hospitals that necessitate closure and costly decontamination.

### NOMENCLATURE

The taxonomy within the genus *Salmonella* is in a continual state of flux. More than 2500 different serotypes (serovars) of *Salmonella* currently exist. The Kauffmann-White scheme originally standardized taxonomy of the genus *Salmonella* according to O- (somatic) and H- (flagellar) antigens, and serovar names were based on the geographic locations where the bacteria were first isolated (e.g., *S. Dublin* or *S. London*). The genus *Salmonella* contains two species—*S. enterica* and *S. bongori*. Six subspecies of *S. enterica* exist: (I) *S. enterica* subsp. *Enterica*, (II) *S. enterica* subsp. *Salame*, (IIIa) *S. enterica* subsp. *Arizonae*, (IIIb) *S. enterica* subsp. *Diarizonae*, (IV) *S. enterica* subsp. *Houte-nae*, and (VI) *S. enterica* subsp. *Indica*. Approximately 60% of *Salmonella* serotypes belong to the *S. enterica* subsp. *Enterica* group, and the within this group, the O-antigen designations A, B, C<sub>1</sub>, C<sub>2</sub>, D, and E account for 99% of all warmblood animal infections. All O-antigen groups have been isolated from *Equidae*, but groups B and D are the most common. The subspecies are further classified into serotypes according to their biochemical differences and their genetic relatedness. Current convention designates

that the serotype name is not italicized and that the first letter is capitalized. Reporting laboratories often abbreviate isolates to genus and serotype instead of the complete form (e.g., *Salmonella* Typhimurium instead of *Salmonella enterica* subsp. *Enterica* serotype Typhimurium).

### EPIDEMIOLOGY

The most commonly reported *Salmonella* serotype isolated from diseased horses is *S. Typhimurium*. The National Animal Health Monitoring System (NAHMS) study reported that *S. Muenchen* was the most common isolate from horses without diarrhea. No enteric host-adapted *Salmonella* spp. exist for horses, which are susceptible to most of the broad host-range *Salmonella* serotypes. Serotypes commonly isolated from clinically diseased horses include Typhimurium, Agona, Anatum, Typhimurium var. Copenhagen, Newport, Infantis, Java, Javiana, Saintpaul, London, Senftenberg, Krefeld, and Miami. Horses are also susceptible to some of the normally host-adapted serotypes of other species, such as *S. Dublin*. *S. Abortusequi* is host-adapted in horses but is more commonly associated with abortion and systemic sepsis in foals rather than with enteric infection and diarrhea; it is not thought to occur in the United States.

The prevalence of fecal shedding of salmonellae by asymptomatic horses varies by geographic location, season, and method of detection. Based on fecal culture, between 1% and 5.5% of horses that were admitted to teaching hospitals without diarrhea shed salmonellae in their feces. This prevalence increases to approximately 17% when polymerase chain reaction (PCR) is used as the method of detection. In one study, more than 60% of horses admitted to a facility for gastrointestinal (GI) disease shed salmonellae in their feces at some point during hospitalization when PCR was used as the method of detection. The recent NAHMS investigation demonstrated a

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that the serotype name is not italicized and that the first letter is capitalized. Reporting laboratories often abbreviate isolates to genus and serotype instead of the complete form (e.g., *Salmonella* Typhimurium instead of *Salmonella enterica* subsp. *Enterica* serotype Typhimurium).

### EPIDEMIOLOGY

The most commonly reported *Salmonella* serotype isolated from diseased horses is *S. Typhimurium*. The National Animal Health Monitoring System (NAHMS) study reported that *S. Muenchen* was the most common isolate from horses without diarrhea. No enteric host-adapted *Salmonella* spp. exist for horses, which are susceptible to most of the broad host-range *Salmonella* serotypes. Serotypes commonly isolated from clinically diseased horses include Typhimurium, Agona, Anatum, Typhimurium var. Copenhagen, Newport, Infantis, Java, Javiana, Saintpaul, London, Senftenberg, Krefeld, and Miami. Horses are also susceptible to some of the normally host-adapted serotypes of other species, such as *S. Dublin*. *S. Abortusequi* is host-adapted in horses but is more commonly associated with abortion and systemic sepsis in foals rather than with enteric infection and diarrhea; it is not thought to occur in the United States.

The prevalence of fecal shedding of salmonellae by asymptomatic horses varies by geographic location, season, and method of detection. Based on fecal culture, between 1% and 5.5% of horses that were admitted to teaching hospitals without diarrhea shed salmonellae in their feces. This prevalence increases to approximately 17% when polymerase chain reaction (PCR) is used as the method of detection. In one study, more than 60% of horses admitted to a facility for gastrointestinal (GI) disease shed salmonellae in their feces at some point during hospitalization when PCR was used as the method of detection. The recent NAHMS investigation demonstrated a

very low level of shedding in the general horse population, with less than 1.0% of cultures from normal horses positive for salmonellae, an incidence that was slightly higher in the southern regions of the United States and during warmer seasons of the year. Although a true carrier state has not been definitively identified in horses, the animals have been shown to harbor the organism within mesenteric lymph nodes. The reported percentage of healthy, nondiarrheic horses with positive lymph nodes is highly variable (between 2% and 70%) and likely reflects geographic diversity.

A number of factors determine infectivity—including serotype, inoculation dose, and host immunity. The number of clinical cases is greatest over the warmer months of the year. Important risk factors for clinical salmonellosis include hospitalization, dietary change, surgery, anesthesia, and antimicrobial use. The challenge inoculum for these “at-risk” horses is tenfold to 1000-fold less than for their immunocompetent cohorts. For these reasons, horses that are admitted to veterinary hospitals, even on an outpatient basis, are susceptible to infection. A horse shedding low levels of salmonellae is not a threat to a healthy adult horse in a low-risk environment. The population at greatest threat is those with GI diseases admitted to referral hospitals for medical or surgical therapy. Within this subpopulation of horses, those with colonic impaction are at highest risk for development of diarrhea, particularly if they receive antibiotics.

Convalescent and postconvalescent shedding in horses is highly variable. Still unclear is whether the shedding patterns of animals treated with antibiotics (either specifically for *Salmonella* infection or as broad-spectrum prophylaxis) is predictably different than those animals treated supportively with only antiinflammatory medications and fluid replacement. Shedding in naturally infected horses, regardless of therapy, ranges from days to months to more than 1 year.

## PATHOPHYSIOLOGY

*Salmonella* infection results in intestinal hypersecretion, the basis of which is not fully understood. The response likely involves a combination of bacterial toxins and a potent host inflammatory reaction associated with bacterial invasion of the epithelium; the latter involves induction of proinflammatory transcription factors and cytokines, including interleukin-1 (IL-1), IL-6, IL-8, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and  $\gamma$ -interferon. Subsequent impairment to mucosal integrity permits absorption of luminal toxins that quickly overwhelm normal clearance mechanisms within the liver and stimulate a classic inflammatory cascade. Inflammation and ulceration of the mucosa is also associated with protein loss, predominantly the low-molecular-weight proteins such as albumin. The resultant reduction in colloid oncotic pressure leads to intestinal edema, which further contributes to intestinal dysfunction.

## CLINICAL SIGNS

The most common clinical manifestation of *Salmonella* infection is diarrhea. The diarrhea is variable in consistency and volume but usually has a characteristic fetid odor.

Hematochezia is rare. Less common enteric syndromes in which *Salmonella* infection is suspected to play a central role include impaction of the small colon, cecal impaction, and diffuse or localized inflammation of the small intestine. Diarrhea may be absent in animals with these conditions.

Colic is a common feature of salmonellosis and often precedes the onset of diarrhea. The pain can be severe but usually subsides as diarrhea develops and increases in frequency and volume. The colic associated with impaction of the small colon or cecum tends to be more persistent. The same may be true if disease is restricted to the small intestine, where pain is associated with enterogastric reflux and gastric distention. Most horses with enterocolitis have increased intestinal sounds in all regions of the abdomen but may experience acute widespread ileus and an absence of borborygmi.

Signs consistent with endotoxemia—including fever, elevated heart and respiratory rates, scleral injection, delayed capillary refill time, and darkening of the visible mucus membranes—are expected in acute cases of salmonellosis. Moderately to severely affected animals may become hypercoagulable, as reflected by deep and superficial venous thrombosis. Laminitis is an unfortunate but relatively common complication of enteric salmonellosis. The signs of laminitis are often delayed for days or weeks after the onset of disease. It is not uncommon for an adult horse to initially demonstrate signs of foot pain after fecal consistency has improved.

Edema of the distal limbs, ventral abdomen, sternum, and head occurs in cases of enteric salmonellosis due to loss of proteins. Edema tends to develop initially in the prepuce in males and migrates to more dependent regions with time.

The disease is particularly debilitating in foals, in which a wide range of clinical signs in addition to diarrhea and fever may occur. These include lameness due to osteomyelitis, synovitis, arterial thrombosis, or laminitis; widespread hair loss (anagen defluxion); neurologic signs due to meningitis; subcutaneous swelling due to rib osteomyelitis or abscesses; discolored urine due to pyelonephritis; or cough associated with pneumonia. Ocular infections are also common in neonatal salmonellosis.

## DIAGNOSIS

Animals with acute salmonellosis usually have a peripheral leukopenia, which is primarily characterized as a neutropenia with shifting to immature forms with toxicity. As the disease progresses or resolves, the leukopenia may be replaced by a mature neutrophilia with a hyperfibrinogenemia. Some horses develop a coagulopathy, which if not controlled progresses into the syndrome of disseminated intravascular coagulation (DIC). Prolongation in prothrombin time and/or partial thromboplastin time, a low platelet count, and an increase in fibrin degradation products support a diagnosis of coagulopathy. A variety of electrolyte changes should be expected, including hyponatremia and hypochloremia. Prerenal azotemia is common, but creatinine and blood urea nitrogen (BUN) should normalize within 24 to 48 hours of fluid therapy. Suckling foals with diarrhea appear to be at a greater risk

for renal failure than do adults, particularly in response to the administration of nephrotoxic agents in the face of persistent dehydration. Mild elevations in hepatobiliary enzymes are also common and are likely secondary to the effects of circulating endotoxins. Large increases in  $\gamma$ -glutamyl transferase (GGT) and alkaline phosphatase can occur with bacterial cholangitis due to ascending infection with salmonellae. Decreases in protein concentration should also be anticipated in moderately to severely affected animals. The total carbon dioxide ( $\text{CO}_2$ ) and calculated bicarbonate concentrations may be low, and animals with circulatory failure will develop a high anion gap acidosis due to accumulation of lactate.

The most definitive method of diagnosis involves isolation of salmonellae from feces, tissue, or body fluid. The recovery of salmonellae from diseased animals with appropriate histories and clinical signs fully supports a diagnosis of salmonellosis. It is important to remember that some animals may shed the organisms in the absence of disease; thus isolation should not always preclude investigation of other causes of diarrhea, including *Clostridium difficile*, *Clostridium perfringens*, or *Neorickettsia risticii*.

### Bacterial Culture

The standard method used to diagnose salmonellosis is through bacterial culture. The likelihood of isolating salmonellae from a fecal sample depends on fecal water content; consequently, infected horses with severe diarrhea will have a greatly diluted inoculum for culture, thus decreasing the sensitivity of the procedure even though salmonellae may be shed in large amounts. Rectal mucosal biopsies may increase the likelihood of organism recovery when fecal volume is high. As expected, the sensitivity of fecal culture appears to increase once fecal consistency improves. Bacterial shedding is often sporadic, even in the clinically diseased animal, thus necessitating the submission of multiple samples for culture. Most clinicians recommend the submission of five fecal samples collected no more frequently than every 12 hours (ideally every 24 hours) to effectively rule in or out salmonellae as the likely causative agent. Isolation of salmonellae from extraintestinal sites is relative to the difficulty in obtaining an *ante mortem* sample (e.g., joint fluid, cerebrospinal fluid [CSF], bone biopsy, blood). Blood culture is an important diagnostic tool in foals younger than 30 days, a population that is frequently bacteremic.

Enrichment procedures and plating on selective media allow for detection and presumptive identification of salmonellae within approximately 48 hours. Enrichment media such as tetrathionate, sodium selenite, or Rappaport-Vassiliadis broth are selectively inhibitory to both gram-positive organisms and most other members of the family Enterobacteriaceae. Dilution of the sample in enrichment media 1:10 v/v as soon as possible after collection and aerobic incubation at 37° C for 18 to 24 hours are recommended; incubations longer than 24 hours diminish the selectivity of the enrichment process. Plating onto selective and differential media permits identification of *Salmonella* spp. based on appearance, as most members of the species produce hydrogen sulfide on common *Salmonella* plating media (e.g., brilliant green agar,

XLD agar, Hektoen-enteric agar, *Salmonella-Shigella* agar). Approximately 13% of *Salmonella* serotypes (some *S. Choleraesuis* and most poultry isolates) give atypical reactions; for example, they may fail to produce hydrogen sulfide or may ferment lactose or sucrose. Therefore at least two different types of plating media should be used. An accredited laboratory such as the National Veterinary Services Laboratories (NVSL) should perform grouping and serotyping.

### Enzyme-Linked Immunosorbent Assay

Commercial enzyme-linked immunosorbent assay (ELISA) kits are available for salmonellae and have historically been used to screen bulk milk samples in dairy herds. The ELISA kits are based on the external O antigen and are therefore serotype-specific. The usefulness of these kits is limited to situations in which the serotype is known or expected.

### Polymerase Chain Reaction

Newer and more sensitive methods of detection include PCR procedures, either alone or in conjunction with traditional enrichment and culture protocols. PCR is highly sensitive but cannot discriminate between live or dead organisms, nor can it differentiate between pathogenic infections and transient bacteria. The major limitations of PCR are that the organism is not available for O-antigen grouping or serotyping and that an antimicrobial sensitivity pattern cannot be determined, which is particularly important when nosocomial infection is suspected.

Quantitative PCR has the advantage of its ability to provide information relative to pathogen number, but its variability is still a concern. One difficulty with PCR is the potential for false-negative results due to the large number of inhibitory compounds present in raw fecal material; therefore samples must usually be extracted before processing.

## TREATMENT

Therapy for the majority of adult horses with salmonellosis is supportive because most infections are self-limiting. Acutely affected animals often require intravenous (IV) replacement of fluid and electrolytes. Therapies directed at combating endotoxemia are also used and include nonsteroidal antiinflammatory drugs (NSAIDs), polymixin B, and pentoxifylline. Horses with chronic diarrhea almost always can maintain their hydration if adequate water and electrolytes are provided.

Colloidal therapy appears to be a key factor in the therapeutic approach to horses with rapidly falling or very low plasma protein concentrations. Generally 6 to 8 L of fresh-frozen plasma is indicated in these animals, but this requirement is expensive. Hydroxyethyl starch (10 ml/kg by IV infusion) is a less costly alternative and is both easier to store and to administer. Serious adverse reactions are rare but include hypersensitivity reactions, circulatory overload, and certain hematologic effects, including disseminated intravascular coagulopathy and hemolysis. Plasma with heparin may be beneficial in animals with suspected coagulopathy.

Orally administered antidiarrheal preparations are commonly used to treat infectious diarrhea, but concerns remain as to dose rate, frequency of administration, and clinical efficacy. Preparations used include adsorbing agents, such as activated charcoal or the hydrous silicate clays (attapulgit, smectite), bismuth subsalicylate, probiotics, and psyllium.

The use of antibiotics in the treatment of salmonellosis is probably the most contentious issue that the veterinarian faces. It is recommended that antibiotics be avoided in uncomplicated cases of enteric salmonellosis, with the following four possible exceptions to this rule:

1. Evidence of extraintestinal infection
2. Foals less than 90 days of age
3. Chronic, recurrent enteric disease
4. The presence of severe leukopenia/neutropenia

Young foals frequently become bacteremic and are at great risk for developing secondary sites of infection. Most of these extraintestinal infections are associated with high mortality even in the face of aggressive antibiotic therapy. Consequently, the role of antibiotics in this group is to prevent the development of secondary sites of infection. Animals that develop chronic intestinal salmonellosis are often treated with antibiotics and immunostimulants to hasten recovery, despite any supportive data. The decision to use antibiotics in severely leukopenic patients is also controversial. The use is often justified as a prophylaxis against other bacterial infections, which occur rarely in horses with *Salmonella* infection. An additional concern, albeit minor, is that antibiotics may in fact predispose these animals to systemic and pulmonary aspergillus infections.

The selection of antimicrobials should be based on culture and sensitivity data. Many clinical isolates demonstrate *in vitro* sensitivity to a wide range of antimicrobials, including chloramphenicol, ampicillin, tetracyclines, trimethoprim/sulfonamide combinations, third-generation cephalosporins, aminoglycosides, and fluoroquinolones. The number of multidrug resistant isolates from horses has increased, including the definitive type 104 strain. Many of these are associated with hospital-acquired infections. The important exceptions are the aminoglycosides and fluoroquinolones. Unfortunately, aminoglycosides are generally ineffective in the treatment of clinical salmonellosis, presumably due to the intracellular location of the bacteria. The fluoroquinolones are active intracellularly, have escaped plasmid-mediated resistance, and therefore remain the drug of choice for the treatment of *Salmonella* infections in humans. Enrofloxacin is the drug of choice in equine practice but must be used with caution in juvenile

animals due to its effects on cartilage. Enrofloxacin (5 mg/kg IV q24h) has been used with some success in foals with *Salmonella* osteomyelitis.

Antibiotics are not indicated for the treatment of carrier animals. In several human studies, antimicrobial therapy did not alter the time course of uncomplicated intestinal salmonellosis, nor did it shorten the duration of postconvalescent shedding. In other studies, antimicrobial therapy was shown to actually prolong fecal shedding in comparison with untreated control patients.

## PREVENTION

Disruptions to normal flora with dietary change, antibiotics, or colonic enterotomy—coupled with any form of stress—are key risk factors in the development of salmonellosis. Most of these factors are difficult to manipulate, especially in a horse with a surgical intestinal lesion. Antibiotics should be used with discretion in all hospitalized animals, particularly in those with preexisting intestinal disease. Steps to limit cross-contamination include sterilization of nasogastric tubes, stall disinfection, and use of environmental cultures. Limited data suggest that prophylactic administration of probiotics does not reduce the risk of salmonellosis, but further studies of alternative preparations and dosages are necessary.

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## CHAPTER 2.9

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# *Rhodococcus equi* Infections

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STEEVE GIGUÈRE

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*Rhodococcus equi*, a gram-positive facultative intracellular pathogen of macrophages, is one of the most important causes of disease in foals between 3 weeks and 6 months of age, with most foals showing clinical signs before the age of 4 months. *R. equi* is a saprophytic inhabitant of soil. Although *R. equi* is present in the environment of all horse farms and antibody is widespread in the horse population, clinical disease is enzootic and devastating on some farms, is sporadic on others, and is unrecognized on most farms. On farms where the disease is enzootic, costs associated with veterinary care, early diagnosis, long-term therapy, and mortality of foals may be high. In addition to significant immediate costs, *R. equi* pneumonia has a long-term detrimental effect on the equine industry because foals that recover from the disease are less likely to race as adults.

### PATHOGENESIS

The farm-to-farm variation in the incidence of the disease likely reflects differences in environmental (temperature, dust, soil pH, soil type) and management (overcrowding, dusty pastures) conditions, as well as differences in the virulence of isolates. Unlike most environmental *R. equi*, isolates from pneumonic foals typically contain an 80 to 90 kb plasmid that encode a family of seven closely related virulence-associated proteins designated VapA and VapC to VapH. Although the total number of *R. equi* in the environment may be similar in farms with or without a history of *R. equi* infections, farms with enzootic disease are more heavily contaminated with virulent (VapA-positive) *R. equi* than are those where the disease is not present. Plasmid-cured derivatives of virulent *R. equi* strains lose their ability both to replicate and to survive in macrophages. Plasmid-cured derivatives also fail to induce pneumonia and are completely cleared from the lungs of foals after heavy intrabronchial challenge, thus confirming the importance of the large plasmid for the virulence of *R. equi*.

Intestinal carriage of *R. equi* in adult horses is likely passive, mainly representing acquisition from contaminated soil. In contrast, the organism actively multiplies in the intestine of foals up to about 3 months of age, reaching numbers up to  $10^5$  per gram of feces. Because pneumonic foals swallow infected sputum, the virulent bacteria can multiply in their intestines. Therefore the manure of *R. equi*-affected foals is likely a major source of progressive contamination of the environment with virulent organisms. Under suitable conditions of high summer temperatures, *R. equi* can multiply in the environment by 10,000-

fold in only 2 weeks. Therefore a single gram of soil that is contaminated with foal manure, under favorable conditions, may contain millions of virulent *R. equi*. Inhalation of dust particles laden with virulent *R. equi* is the most important route of pneumonic infection in foals. Ingestion of the organism is a significant route of exposure and immunization but does not lead to hematogenously acquired pneumonia unless the foal has multiple exposures to very large numbers of bacteria.

### CLINICAL MANIFESTATIONS

The most common manifestation of *R. equi* infections in foals is a chronic suppurative bronchopneumonia with extensive abscessation. The slow spread of lung infection, coupled with the remarkable ability of foals to compensate for progressive loss of functional lung, make early clinical diagnosis difficult. Early clinical signs may only include a slight increase in respiratory rate and a mild fever. These subtle clinical signs are often either missed or ignored, allowing the condition to progress. Therefore even with the chronic form of the disease, respiratory signs are often of apparently acute onset. As the disease progresses, clinical signs may include decreased appetite, mild lethargy, fever, tachypnea, and increased effort of breathing characterized by nostril flaring and increased abdominal effort. Cough and bilateral nasal discharge are inconsistent findings. Most affected foals are in good body condition, but weight loss may become apparent with chronicity in severely affected individuals.

Approximately half of pneumonic foals presented for necropsy also have abdominal lesions. However, the vast majority of foals with *R. equi* pneumonia do not show clinical signs of intestinal disease. The intestinal form of *R. equi* infection is characterized by a multifocal ulcerative enterocolitis and typhlitis over the area of the Peyer's patches, with granulomatous inflammation of the mesenteric and/or colonic lymph nodes. Occasionally, a single large abdominal abscess is the only finding. These foals have a poor prognosis because at the time of diagnosis extensive adhesion of the large or small intestine to the abscess often is seen. Clinical signs associated with the abdominal form of the disease may include fever, depression, anorexia, weight loss, colic, and diarrhea.

Polysynovitis, particularly of the tibiotarsal and stifle joints, is seen in approximately one third of cases with *R. equi* pneumonia. Occasionally all joints are affected. The degree of joint effusion varies, and in most cases, lame-

ness is not apparent or is limited to a stiff gait. Cytologic examination of the synovial fluid usually reveals a non-septic mononuclear pleocytosis, and bacteriologic culture of the synovial fluid usually fails to yield an agent. This polysynovitis is believed to be immune-mediated and usually resolves as pneumonia resolves, with antimicrobial therapy. The presence of a nonseptic polysynovitis in a foal between 1 and 6 months of age suggests *R. equi* infection. Immune complex deposition may also contribute to the development of uveitis, anemia, and thrombocytopenia in some foals.

Bacteremic spread of the organism from the lungs or gastrointestinal (GI) tract may occasionally result in septic arthritis and/or osteomyelitis. However, foals can occasionally develop *R. equi* septic arthritis or osteomyelitis without apparent lung or other source of infection. The degree of lameness of foals with septic arthritis distinguishes them from foals with immune-mediated polysynovitis. In equivocal cases, bacterial culture and cytologic examination of the synovial fluid should be performed. Foals with *R. equi* osteomyelitis usually show signs of lameness and swelling over the affected area. The extension of bone infection through the metaphyseal cortex and into surrounding tissue may lead to cellulitis and sometimes septic arthritis.

In addition to appropriate antimicrobial therapy (see the discussion of treatment), foals with *R. equi* septic arthritis and osteomyelitis often require aggressive local therapy and have a guarded prognosis. *R. equi* vertebral osteomyelitis has also been reported. Early signs of vertebral osteomyelitis are often limited to fever, lethargy, stiff gait, reluctance to move, and resistance to palpation. However, the diagnosis is rarely made until the infection extends to the epidural space, causing signs of spinal cord or nerve compression. Such signs may include paresis, ataxia, paralysis, or cauda equina syndrome, depending on the severity and site of compression.

Ulcerative lymphangitis, cellulitis, and subcutaneous abscesses also have been reported. Other rare manifestations of *R. equi* infections in foals include panophthalmitis, nephritis, and hepatic and renal abscessation. Disease due to *R. equi* is rare in adult horses and is sometimes associated with immunosuppression. Sporadically occurring illness that is similar to that in foals and that primarily involves lungs, colon, related lymph nodes, and (rarely) wound infection has been discussed in a few reports. In rare instances the organism also has been isolated from infertile mares and aborted fetuses.

## DIAGNOSIS

The distinction between lower respiratory tract infections caused by *R. equi* and those caused by other pathogens is problematic, especially on farms with no previous history of *R. equi* infections. Many diagnostic tests—including complete blood count (CBC), measurement of fibrinogen concentrations, and radiographs or ultrasound of the chest—may help distinguish *R. equi* pneumonia from that caused by other pathogens. However, bacteriologic culture or polymerase chain reaction (PCR) amplification, combined with cytologic examination of a tracheobronchial aspirate (TBA), is the only way to make a definitive diagnosis.

Cytologically, intracellular gram-positive coccobacilli can be identified in approximately 60% of foals in which *R. equi* is cultured from a TBA. Foals without clinical disease exposed to contaminated environments may have *R. equi* in their tracheas as a result of inhalation of contaminated dust. For this reason, bacteriologic culture of a TBA should be interpreted in the context of cytologic evaluation, physical examination, and laboratory results. A light growth of *R. equi* from a foal with normal fibrinogen concentrations and white blood cell (WBC) count and no clinical signs of respiratory disease or cytologic evidence of airway inflammation is likely an incidental finding. Nucleic acid amplification based on the VapA gene sequence by PCR is a slightly more sensitive means to identify *R. equi* in TBA samples than is bacterial culture, especially if the sampled foal is concurrently being treated with antimicrobial agents. PCR amplification may be done in association with—but should not replace—bacterial culture because it does not permit identification of concurrent bacterial pathogens and *in vitro* antimicrobial susceptibility testing. Other pathogens are often isolated along with *R. equi*.

Hyperfibrinogenemia and neutrophilic leukocytosis are the most consistent laboratory findings in foals with *R. equi* pneumonia. Foals with *R. equi* pneumonia tend to have higher fibrinogen concentrations and leukocyte counts than foals from which other pathogens are isolated. However, individual variation precludes the use of fibrinogen concentrations and WBC as diagnostic tests or prognostic indicators for an individual animal.

Thoracic radiography and ultrasonography are useful in the evaluation of the severity of pneumonia and the assessment of response to therapy. A prominent alveolar pattern characterized by ill-defined regional consolidation is the most common radiographic abnormality. The consolidated lesions are often seen as more discrete nodular and cavitory lesions compatible with pulmonary abscessation. Ultrasonography is a helpful diagnostic tool when lung involvement includes peripheral areas. In *R. equi*-infected foals, ultrasonographic evaluation of the chest often reveals extensive consolidation with well-defined abscesses. Ultrasonography is also a useful tool for detection of abdominal abscesses in some cases. In foals less than 4 months of age, radiographic or ultrasonographic evidence of nodular lung lesions suggests *R. equi* infections. However, *Streptococcus equi* subsp. *zooepidemicus* is another common cause of lung abscesses, especially in foals that are 4 months of age or older.

The serologic diagnosis of *R. equi* infections is problematic because the widespread exposure of foals to this organism at a young age leads to antibody production without necessarily the production of clinical disease. In addition, maternally derived antibody may cause positive reactions in some serologic assays, which further confound the interpretation of the test. Simple reliance on serology as a diagnostic test for *R. equi* infections results in overdiagnosis of the disease and in missing infections in the early stages. Serologic tests such as agar gel immunodiffusion (AGID) and enzyme-linked immunosorbent assay (ELISA) may be useful at the farm level to detect overall exposure, but they have no value in the diagnosis of clinical *R. equi* infections on enzootic farms.



## TREATMENT

A wide variety of antimicrobial agents are effective against *R. equi in vitro*. However, because *R. equi* is an intracellular pathogen that survives and replicates in macrophages and that causes granulomatous lesions with thick caseous material, many of these drugs are ineffective *in vivo*. The combination of erythromycin and rifampin has been used extensively for the treatment of *R. equi* infections in foals and has dramatically reduced foal mortality since its introduction. Their use in combination reduces the likelihood of resistance to either drug. The recommended dosage regimen for rifampin is 5 mg/kg every 12 hours or 10 mg/kg every 24 hours, taken orally. Rifampin may cause urine and other secretions (tears, saliva, etc.) to turn red-orange but is usually well-tolerated when administered orally for long period of time. The recommended dosage regimen for erythromycin is 25 mg/kg every 6 to 8 hours, taken orally. Resolution of clinical signs, normalization of plasma fibrinogen, and radiographic resolution of lung lesions are commonly used to guide the duration of therapy, which generally ranges between 4 and 9 weeks. Long-term therapy is expensive but essential because relapses may occur if therapy is discontinued early. Additional gram-negative antimicrobial coverage is recommended in foals from which a resistant gram-negative pathogen is also isolated in significant numbers from a TBA. The combination of gentamicin or amikacin with erythromycin or rifampin *in vitro* gives significant antagonistic activity against *R. equi*. Therefore concurrent administration of an aminoglycoside with either erythromycin or rifampin for the treatment of *R. equi* infections is not recommended.

Although it is well-tolerated by most foals, erythromycin commonly causes diarrhea. In several foals, diarrhea is mild and self-limiting and does not necessitate cessation of therapy. However, diarrheic foals should be monitored carefully because they may develop depression and severe diarrhea, thus leading to dehydration and electrolyte loss that necessitate intensive fluid therapy and cessation of oral erythromycin. During surges of very hot weather, an idiosyncratic reaction characterized by severe hyperthermia and tachypnea has been described in foals treated with erythromycin. Administration of antipyretic drugs and placement of the foal in a cold environment helps treat this problem. Diarrhea also has been observed occasionally in the dams of nursing foals while the foals are being treated with oral erythromycin, presumably because coprophagic behavior leads to ingestion of sufficient active erythromycin to perturb the intestinal flora of the mare and allow overgrowth of *Clostridium difficile*. Although the vast majority of *R. equi* isolates from foals are sensitive to erythromycin and rifampin, resistant strains to either drug have been encountered. Therapy for foals that are infected with resistant isolates or that develop severe complications after therapy with erythromycin is problematic because of the limited range of alternative effective drugs.

High doses of the trimethoprim-sulfonamide (TMS) combination (30 mg/kg of combination q8-12h orally) alone or in combination with rifampin may be effective in foals with mild or early *R. equi* pneumonia without marked evidence of pulmonary abscessation or for con-

tinued therapy in foals responding well to other antimicrobial agents. However, TMS is unlikely to be as effective as erythromycin and rifampin for the treatment of severe *R. equi* pneumonia with extensive abscessation because of its poor activity in caseous material and against most intracellular pathogens. Chloramphenicol can also be administered orally and achieves high concentrations within phagocytic cells. The recommended dosage regimen is 50 mg/kg every 6 hours, given orally. However, the potential human health risk and the fact that only 70% of *R. equi* isolates are susceptible to this drug make it a less-attractive alternative.

Azithromycin and clarithromycin are two newer-generation macrolides commonly used in human medicine. Compared to erythromycin, they are more chemically stable, have a greater bioavailability, and achieve higher concentrations in phagocytic cells and tissues. Based on the pharmacokinetic parameters in foals and on *in vitro* minimum inhibitory concentration (MIC) of *R. equi* isolates, azithromycin (10 mg/kg orally q24h for 5 days followed by q48h therapy) or clarithromycin (7.5 mg/kg q12h orally) would be appropriate for the treatment of *R. equi* infections in foals. Although controlled studies are required to confirm the efficacy and safety of these dosages, clinical experience suggests that azithromycin or clarithromycin, in combination with rifampin, are effective for treatment of *R. equi* infections in foals and are better tolerated than erythromycin.

## PROGNOSIS

Before the introduction of the combination erythromycin-rifampin as the recommended treatment, the prognosis of *R. equi* pneumonia was poor, with a reported mortality rate as high as 80%. A successful outcome (as assessed by survival) from the use of erythromycin and rifampin has been reported in approximately 70% to 80% of foals with *R. equi* pneumonia. Death is more likely in foals with respiratory distress. In one study that evaluated the effect of *R. equi* pneumonia on future racing performance, 54% of survivors had at least one racing start, as opposed to 65% for the control foal population, which suggests that horses that contract *R. equi* pneumonia as foals are slightly less likely to race. However, those foals that raced performed as well as the control population.

## PREVENTION

### Decreasing the Size of Infective Challenge

Infection progressively builds up on horse farms that are in prolonged use so that enzootic farms are likely to be those used for breeding horses for many years; those with heavy concentrations of mares and foals; and those located where summer temperatures are high, where the soil type is sandy, and where dust is extensive. Large numbers of foals kept on bare, dusty, manure-containing paddocks will result in heavy challenge, with clinical disease maintaining virulent bacteria. Although environmental conditions are major contributing factors, they are often impossible to alter. Housing foals in well-ventilated, dust-free areas and avoiding dirt paddocks and crowding is impor-

tant. Pasture must be rotated to decrease dust formation and consequent inhalation of *R. equi*. Any sandy or dirt areas ideally should be planted with grass and made "off limits" to foals. Alternatively, irrigation may help decrease dust formation. Infected foals should be isolated because they are the major source of contamination of the environment with virulent bacteria.

### Early Recognition of the Disease

Early recognition of *R. equi* cases and isolation and treatment of infected foals reduce losses, prevent the spread of virulent organisms, and limit the cost of therapy on farms where the disease is devastating. For this reason a combination of careful daily observation and measurement of WBC counts and plasma fibrinogen concentrations on all the foals at 2- to 4-week intervals, although labor-intensive, is a useful approach to early identification of *R. equi*-infected foals on enzootic farms. Periodic ultrasonographic examination of the chests of all the foals on enzootic farms (starting at 3-4 weeks of age) is also useful in early identification of pneumonic foals before clinical signs begin to develop. Ultrasonography also offers the advantage of evaluation of the severity of lung involvement and assessment of response to therapy.

### Passive Immunization

Intravenous (IV) administration of hyperimmune (HI) plasma obtained from horses vaccinated against *R. equi* with various antigens has consistently proved effective in significantly reducing the severity of *R. equi* pneumonia in foals after experimental challenge. However, results of studies that evaluated the efficacy of various HI plasma preparations under field conditions have proved contradictory. These contradictions suggest that various factors—such as the method by which plasma donors are immunized, the amount of HI plasma used, the timing of HI plasma administration, management conditions, and the number of virulent bacteria in the environment—may influence the effectiveness of a particular HI plasma product. Recent research suggests that antibodies to VapA and VapC proteins, which are present in most HI plasma preparations, are important in protection.

Administration of HI plasma before infection with *R. equi* is essential. However, early administration may result in the decline of passively transferred antibody to a non-

protective level at a time when foals are still susceptible to *R. equi* and when environmental challenge is high. Therefore IV administration of 1 L of HI plasma within 48 hours of birth, followed by a second administration at approximately 25 days of age, may be the best approach on farms with high morbidity rates. A single administration at the beginning of the warm season may be sufficient for foals born early during the year in geographic areas where cold winter temperatures reduce environmental challenge. These recommendations are only guidelines, and the best time for administration of HI plasma may in fact vary by the geographic location of the farm, the size of infective challenge, and the age at which most foals on the farm develop clinical signs.

HI plasma for the prevention of *R. equi* pneumonia is commercially available in North America (Lake Immunogenics, Inc., Ontario, N.Y.; Veterinary Dynamics, Inc., Templeton, Calif.). HI plasma is expected to slightly decrease the incidence of the disease (by 30%-40%) but does not prevent infection in all foals and should not lull farm owners into a false sense of security and reduce the need for continued vigilance. Whether this strategy is cost-effective varies from farm to farm. If used for the control of control of *R. equi* infections on enzootically infected farms, administration of HI plasma should always be combined with other control strategies, such as attempts to decrease the size of infective challenge and early identification and treatment of infected foals.

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## CHAPTER 2.10

# Strangles

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### ETIOLOGY AND CLINICAL SIGNS

Equine strangles is a highly contagious disease of the upper respiratory tract caused by infection with *Streptococcus equi*, a gram-positive, Lancefield group C,  $\beta$ -hemolytic bacterium with a worldwide distribution. The disease has an incubation period between 3 and 14 days, depending on infectious dose and the host's immune status. Initial clinical signs include marked pyrexia (103°-106° F) associated with depression and inappetence. Affected horses invariably develop a serous nasal discharge that soon becomes purulent and profuse, and some develop a soft, moist cough and/or purulent ocular discharge.

Strangles is classically characterized by a lymphadenitis associated with rapid metastasis of *S. equi* infection from buccal and nasopharyngeal mucosal surfaces to the draining lymph nodes of the head and neck, which probably occurs within hours of infection. Submandibular lymph nodes (SMLN) and parotid lymph nodes (PLN) become palpably firm, swollen, and painful, and with abscessation of these and the retropharyngeal lymph nodes (RPLN), the pharynx becomes obstructed, thus causing difficulty in breathing (hence the name *strangles*). Approximately 1 to 2 weeks after clinical signs first appear, the abscessed lymph nodes usually develop sinuses and rupture their purulent contents through either the skin (SMLN and PLN) or into the guttural pouches (RPLN). This stage of the disease often coincides with a sudden and marked clinical improvement. Rupture of the RPLNs results in guttural pouch empyema that may subsequently drain into the pharynx through the pharyngeal pouch opening, the lowest part of the pouch, when the horse lowers its head to the ground. This discharge is either swallowed or flows down the nose to appear as a profuse purulent nasal discharge. Lymph nodes of the head may abscess sequentially so that in most cases the entire clinical course of disease may last several weeks, although not all infected animals in outbreaks necessarily show typical signs. Morbidity rates of 100% are not uncommon in susceptible populations, and mortality rates of 8% to 10% have been reported among cases, although rates are usually much lower in well-managed animals. In addition to the usual clinical signs of strangles, serious complications occur in as many as 20% of cases.

"Bastard" strangles describes the systemic spread of *S. equi* infection to and subsequent abscessation of any part of the body other than the lymph nodes of the head. A wide range of organs and distal lymph nodes may become infected by metastasis of the infection—including the

lungs; liver; spleen; kidneys; brain; spinal cord; joints; endocardium; and the cervical, pulmonary, prescapular, mediastinal, and mesenteric lymph nodes. Abscesses also can occur paravertebrally or cutaneously in the periorbital, perianal, and facial regions and on the limbs. Purpura hemorrhagica is an acute, immune-mediated condition that is usually seen in older horses and is characterized by vasculitis, well-demarcated subcutaneous edema—particularly of the head and limbs—and petechial hemorrhages of mucosae, musculature, and viscera. Evidence suggests that immune complexes that contain the surface M-protein antigen of *S. equi* are involved in the pathogenesis of purpura. The vasculitis may be widely distributed throughout the body and affect many organs, including the muscles, heart, gastrointestinal (GI) tract, kidneys, and lungs. The resulting peripheral edema may be so severe as to cause fatal circulatory collapse.

### DIAGNOSIS

A strongly presumptive diagnosis of strangles may be made on clinical grounds in horses that demonstrate lymph node abscessation, although lymphadenitis may only occur in later cases or may remain clinically inapparent in some outbreaks. However, in these apparently nontypical strangles outbreaks, earlier abscessation of RPLNs in some horses may be confirmed by the detection of guttural pouch empyema on endoscopic examination.

To maximize the chance of effective containment and to control outbreaks, a definitive diagnosis must be made as early as possible, even in horses that may not have classic signs. This diagnosis is best achieved through isolation of *S. equi* from appropriate samples, such as pus aspirated from lymph nodes and swabs or washings from discharging abscesses and the nasopharynx, preferably from a large representative sample. However, care should be taken with the interpretation of negative laboratory results, especially from horses that demonstrate typical signs of strangles. Draining abscesses quickly become colonized by other bacteria that often overgrow and mask *S. equi*. Furthermore, a negative result on a single short nasal swab from one horse should not be taken as assurance that *S. equi* is not involved because mucosal colonization may be short-lived. Moreover, as with draining abscesses, the background flora is complex, and the presence of *S. equi* may be hidden. Consequently, it is always wise to follow the general rule of thumb that if it *looks* like strangles, then it *probably is* strangles.

Conventional culture and differential identification by sugar fermentation remain the cornerstone of definitive diagnosis of *S. equi* infection. *S. equi* is conventionally identified by the inability of subcultures of its hemolytic colonies to ferment ribose, sorbitol, trehalose, and lactose when inoculated into serum sugar broths and by possession of the Lancefield group C antigen in a latex agglutination test. Importantly, however, recently developed polymerase chain reaction (PCR) assays are being used increasingly in conjunction with culture to improve the sensitivity of detection of *S. equi*, especially in outwardly healthy but potentially infected horses that pose a risk of transmission if they are in close contact with susceptible animals. PCR tests have been developed for detection of the DNA of the M-protein gene and 16S-23S RNA gene intergenic spacer, which in combination are able to differentiate *S. equi* from the vast majority of subtypes of the ubiquitous but closely related *Streptococcus zooepidemicus* species.

A diagnosis of bastard strangles should initially be suspected with the presentation of overt and unusual clinical signs in any animal that is known to be either currently suffering or has recently recovered from or has had contact with strangles. Although it is often fairly nonspecific, bastard strangles may be symptomatic of the anatomic site(s) of infection and may include increased respiratory effort, periodic pyrexia, depression, inappetence, intermittent colic, or chronic weight loss. Additional and appropriate diagnostic techniques—including hematology (usually revealing leukocytosis with mature neutrophilia and left shift), clinical chemistry (raised serum globulin and fibrinogen), and peritoneal and/or pleural fluid collection (raised white blood cell count, protein and fibrinogen, intracellular and extracellular cocci on a stained smear despite often negative bacteriologic culture)—may help to confirm the presence and site of *S. equi* abscessation.

Rectal examination (with or without transrectal or transabdominal ultrasound) may reveal an abnormal abdominal mass, palpation of which is generally resented. Exploratory laparotomy or laparoscopy may reveal the presence of abdominal abscesses. Sometimes the diagnosis can only be made at necropsy in animals found dead or after elective euthanasia for intractable idiopathic disease. Isolation of *S. equi* from abscesses provides a diagnosis of bastard strangles. Diagnosis of purpura hemorrhagica is generally made on the basis of typical clinical signs, which usually appear between 2 and 4 weeks after an apparent resolution of strangles or after administration of a strangles vaccine.

## EPIDEMIOLOGY

Purulent discharges from active and recovering strangles cases are an extremely important and easily recognizable source of new *S. equi* infections in susceptible horses. Transmission of infection occurs with direct or indirect transfer of these purulent discharges that carry *S. equi* between affected and susceptible horses. Direct transmission refers to horse-to-horse contacts, particularly through normal equine social behavior that involves mutual head contact. Indirect transmission occurs through the sharing of con-

taminated housing, water sources, feed or feeding utensils, twitches, tack, and other less-obvious fomites, such as the clothing and equipment of handlers and veterinarians and, anecdotally, even via other species of animal. The organism has the ability to remain viable and infectious in the environment for prolonged periods if maintained in moist discharges, particularly if protected from chemical disinfectants and sunlight.

Transmission that originates from outwardly healthy animals is increasingly recognized as probably being of greater importance than from purulent discharges from sick horses because the source of infection is hidden and appears without warning. One obvious group of potentially infectious but outwardly healthy horses includes those that are incubating the disease and go on to develop signs themselves. Normal nasal secretions are assumed to be the source of infection in these animals. The other important category of outwardly healthy but potentially infectious horses is those animals that continue to harbor the organism after full clinical recovery. Evidence suggests that a moderate proportion of horses continue to harbor *S. equi* for several weeks after clinical signs have disappeared, even though the organism is no longer detectable in the majority of horses 4 to 6 weeks after total recovery. Therefore considering all recovered horses as potential sources of infection for at least 6 weeks after their purulent discharges have dried up is sensible.

Alarming, carriage and at least periodic shedding of *S. equi* continues for prolonged periods after apparent full and uncomplicated recovery in a subcategory of outwardly healthy but potentially infectious horses. These horses are referred to as *long-term, asymptomatic S. equi carriers*, and anecdotal evidence strongly suggests that they can be a significant source of new outbreaks, even in well-managed groups of horses. Fully effective control measures require appropriate detection and management of this important category of animal.

Short-lived guttural pouch empyema is likely the most frequent outcome of uncomplicated drainage of RPLN abscessation. However, in a small but significant proportion of cases (i.e., >10% in three intensively investigated recent U.K. outbreaks) this clearance mechanism fails, thus resulting in chronic empyema of the pouch. In some horses, guttural pouch empyema with *S. equi* infection may persist asymptotically for many months or even years. In these long-standing cases, pus in the pouches inspissates and then eventually forms into discrete, ovoid, smooth concretions known as *chondroids*. Chondroids may occur singly or as multiples, sometimes in very large numbers. In chondroids formed after strangles, *S. equi* can be cultured and demonstrated histologically on the surface and on lining fissures within their structure.

Identification, segregation, and treatment of these potentially infectious horses has successfully controlled prolonged outbreaks and undoubtedly prevented further outbreaks. A systematic program of repeated nasopharyngeal swabbing (i.e., at least three swabs taken at weekly intervals) of horses after the cessation of clinical signs or during quarantine of incoming horses, using conventional culture in conjunction with PCR, has successfully identified carrier horses. Confirming the diagnosis of guttural pouch empyema is generally straightforward and is best achieved

by direct visual assessment of the inside of both pouches by endoscopy. Cytologic assessment and culture and PCR of *S. equi* in lavage samples collected through the endoscope should always accompany this visual examination, as infection and inflammation may persist in the absence of overt, visible pathologic processes. The diagnosis of guttural pouch empyema and chondroids may also be made by radiography of the head, and *S. equi* may be cultured from lavages collected by direct percutaneous sampling of the pouch.

During recent intensive outbreaks, investigations that used repeated nasopharyngeal swabbing and guttural pouch endoscopy, variants of *S. equi* have been discovered in a significantly higher proportion of carriers (24%) than clinical cases of strangles (<1%). The variants lacked DNA coding for up to 20% of the surface-expressed M-protein and were shown to express truncated forms of this protein in comparison to nonvariant *S. equi*. The fact that variants were much more prevalent in outwardly healthy horses than those with signs of strangles possibly suggests that the variants represented a less virulent but immunizing form of *S. equi* and as such may have contributed to herd immunity by acting as a natural, live vaccine. However, experimental infection has shown that variant *S. equi* that express a truncated M-protein appear equally pathogenic as strains with the full M-protein and demonstrate that at the present time all carriers should be regarded as potential sources of new strangles outbreaks.

## CONTROL OF OUTBREAKS

Veterinary investigation of strangles outbreaks should begin by interview with horse owners and attending veterinarians for a detailed history and to evaluate the potential full extent of the disease problem. The review should identify affected groups of horses and allow the geography of the premises and the management practices adopted on them to be assessed for further risks and future opportunities for disease control. A practical disease-control strategy should then be agreed upon and implemented. The general aims and measures for such a strategy are outlined in Table 2.10-1. This outline strategy may need to be adapted to the individual circumstances of each specific premises and outbreak.

In summary, all movements of horses on and off the affected premises should be stopped, and parallel segregation and hygiene measures should be implemented immediately. Cases of strangles and their contacts should be maintained in well-demarcated “dirty” (i.e., *S. equi*—positive) quarantine areas. The aim of the control strategy, following bacteriologic screening, is to move horses from the “dirty” to the “clean” areas, where nonaffected and noninfectious horses are kept. Every care should be taken to ensure high standards of hygiene throughout the premises for the duration of the investigation. Screening of all convalescing cases and their healthy contacts should be conducted via swab or lavage of the nasopharynx, with special care taken to maintain good hygiene to avoid inadvertent transmission among horses during sampling.

Swabs or lavages are taken at weekly intervals over several weeks and are tested for *S. equi* by conventional culture and PCR. Because PCR can detect both dead and liv-

ing bacteria, positive PCR results are regarded as provisional and subject to further investigation. The vast majority of asymptomatic, long-term carriage of *S. equi* occurs in the guttural pouches of recovered horses. Therefore endoscopy of the upper respiratory tract and guttural pouches should be performed in all outwardly healthy horses in which *S. equi* is detected, either by culture or PCR. Lavage samples from guttural pouches should then be tested for *S. equi* by culture and PCR. However, other sites, such as the nasal sinuses or trachea, should be considered in horses that continue to harbor *S. equi* in the absence of pathologic processes or *S. equi* infection of the guttural pouches.

## TREATMENT

The only treatment usually required for the majority of strangles cases is provision of a dry, warm environment; palatable, easily swallowed food; and good-quality nursing care. Abscesses should be encouraged to mature and discharge by use of poultices and lancing, followed by frequent flushing with 3% to 5% dilute povidone-iodine solution until purulent discharges cease. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as phenylbutazone (4.4 mg/kg/day) and flunixin meglumine (1.1 mg/kg/day) should also be administered, as appropriate, to reduce the pyrexia, pain, and inflammation associated with *S. equi* infection and to consequently improve demeanor and maintain appetite. Lancing of abscesses and emergency surgical tracheostomy may be required when acute respiratory obstruction occurs.

The value of antibiotic treatment in strangles is controversial. Although *S. equi* is fully susceptible to almost all the antimicrobials that are commonly used in horses, their effectiveness *in vivo* may be extremely poor, especially when infection has migrated to the lymph nodes or in the case of guttural pouch empyema. Furthermore, problems with recurrence of lymphadenitis and subsequent abscessation sometime after the cessation of treatment are common. Although it is commonly cited that use of antibiotics increases the risk of bastard strangles, very little supporting scientific evidence to this end exists, and this severe complication occurs in outbreaks in which no treatment has been used.

Use of antimicrobials may instill a false sense of security that animals are no longer infectious and thus that strict hygiene measures are no longer necessary. Consequently, the use of antibiotics in strangles outbreaks should be considered carefully. If antimicrobials are used, continued close clinical monitoring of animals for several weeks after the end of antibiotic administration, during which the highest standards of hygiene should be maintained, is strongly recommended. If antimicrobial treatment is to be used for strangles, penicillin—typically procaine penicillin (22,000 IU/kg IM q24h)—remains the antibiotic of choice for *S. equi*. Alternatively, ceftiofur (2.2 mg/kg IM q24h) or trimethoprim-potentiated sulfonamide (30 mg/kg PO q12h) can be used for more extended periods.

Treatment of bastard strangles is most feasible when abscesses are accessible so that they can be drained and flushed with dilute povidone-iodine. A prolonged course

**Table 2.10-1**  
**Aims and Measures to Control Transmission of *Streptococcus equi* on Affected Premises**

Aim	Measure
1. To prevent spread of infection to horses on other premises and to new arrivals on the affected premises	All movement of horses on and off the affected premises should be stopped immediately until further notice.
2. To establish whether horses are infectious in the absence of clinical signs of strangles (i.e. asymptomatic carriers)	All recovered cases and contacts should have at least three nasopharyngeal swabs or lavages taken at approximately weekly intervals and tested for <i>S. equi</i> by culture and PCR.
3. To determine whether horses are likely to be free from infection with <i>S. equi</i> (i.e., noninfectious for strangles)	Three consecutive swabs or lavages should be negative for <i>S. equi</i> by culture and PCR.
4. To determine whether horses are likely to be harboring <i>S. equi</i> (i.e., infectious for strangles)	<i>S. equi</i> is cultured or detected by PCR on any of the screening swabs. (Horses with only positive PCR results are considered <i>provisionally positive</i> subject to further tests.)
5. To prevent direct transmission of infection by isolation of infectious horses from those screened negative for <i>S. equi</i>	Infectious horses are maintained in so-called dirty (i.e., <i>S. equi</i> -positive) isolation areas that are physically cordoned from the other "clean" areas of the premises where noninfectious horses are kept. Clustering of cases in groups should allow parts of the premises to be easily allocated as "dirty" and "clean."
6. To prevent indirect cross-infection from horses in the "dirty" area to those in the "clean" area of the premises	Potentially infectious horses in the "dirty" area are preferably looked after by dedicated staff members or are dealt with <i>after</i> noninfectious horses in the "clean" area. Strict hygiene measures are introduced, including provision of dedicated clothing and equipment for each area, disinfection facilities for personnel, and thorough stable cleaning and disinfection methods.
7. To monitor horses in the "dirty" areas for persistence of <i>S. equi</i> infection and to establish sites of carriage of infection	Nasopharyngeal swabbing or lavages are continued, with endoscopic examination of the upper respiratory tract, including guttural pouches in those horses in which <i>S. equi</i> was detected after clinical signs had disappeared. Horses that satisfy the noninfectious criteria of step 3 or have at least the third swab of the series negative by PCR (to allow for possible persistence of PCR-positive but dead bacteria) are returned to the "clean" area.
8. To eliminate inflammation and <i>S. equi</i> infection from the guttural pouches and other sites (see text discussion of treatment)	The products of the pathologic process are removed through a combination of flushing and aspiration of saline, and chondroids are removed with endoscopically guided instruments. Penicillin antimicrobial treatment is administered topically and systemically to eliminate <i>S. equi</i> infection.

PCR, Polymerase chain reaction.

of parenteral procaine penicillin (dose as stated previously) should be started and administered daily. Alternatively, oral antimicrobial treatment such as trimethoprim-potentiated sulfonamide can be used for longer periods of treatment. Other appropriate symptomatic treatment, such as analgesics (e.g., butorphanol [0.05-0.1 mg/kg], meclufenamic acid [2.2 mg/kg q24h], phenylbutazone [4.4 mg/kg q24h]) and flunixin meglumine (1.1 mg/kg q24h), may be administered where indicated. The diagnostic techniques described previously may be useful in monitoring for remission of abscessation during and after treatment.

Treatment of purpura hemorrhagica is aimed at the following objectives:

1. Removing the antigenic stimulation
2. Reducing the exaggerated immune response

### 3. Reducing blood vessel wall inflammation

#### 4. Providing supportive therapy

Some reports have proposed that these goals may be achieved by use of procaine penicillin to treat the *S. equi* infection and the use of intravenous (IV) corticosteroids such as dexamethasone (up to 0.2 mg/kg) to suppress the immune response and reduce vessel wall inflammation. However, treatment with penicillin is controversial because it may result in bacterial cell lysis that could increase the amount of circulating M-protein, which may potentially exacerbate immune complex formation and consequently worsen clinical disease. Supportive care, such as leg wraps, light walking exercise, hydrotherapy, diuretics, and IV fluid administration should be used as necessary.

Appropriate methods of treatment for guttural pouch empyema in individual horses depend on the consistency

and volume of the material within the pouches. Repeated lavages of pus-filled pouches via rigid or indwelling Foley catheters with saline or dilute povidone-iodine solution and with subsequent lowering of the head to allow drainage or use of a suction pump attached to the endoscope help eliminate empyema. Administration of both topical and systemic procaine penicillin greatly improves the success rate of treatment. Topical installation of 20% (w/v) acetylcysteine solution has also been used to help treat empyema. Acetylcysteine has a denaturing/solubilizing activity by disrupting disulfide bonds in mucoprotein molecules, thus reducing mucus viscosity and facilitating natural drainage.

In more long-standing cases, inspissation of the purulent material produces a thickened empyema and chondroids that do not readily drain into the pharynx. These cases are more difficult to treat topically, as they can be refractory to large-volume irrigation. Furthermore, early attempts at removal with endoscopically guided instruments have been technically more difficult and time-consuming. Conventional treatment of such cases has been by surgical hyovertibrotomy and ventral drainage through Viborg's triangle. This technique, however, carries all the inherent risks of a general anesthetic and surgical dissection around the major blood vessels and nerves of the region, as well as the possibility of *S. equi* contamination of the hospital environment. More recently, use of improved sedation and endoscopic techniques—especially a memory-helical polyp retrieval basket through the biopsy channel of the endoscope—has permitted nonsurgical removal of chondroids, even in very large numbers and in conjunction with empyema. When combined with topical and systemic antimicrobial therapy, this technique is usually sufficient for successful treatment of even the most severe guttural pouch pathologic process.

## PREVENTION

Although much more preferable to the control of outbreaks, prevention of strangles is usually very difficult to achieve, especially without specific measures to reduce the risk of inadvertent introduction of *S. equi* infection through asymptomatic carriers. Prevention is particularly difficult when horses are frequently moved and intermixed and when strangles outbreaks have not been appropriately investigated and controlled. Wherever possible, animals that are being introduced to a new population of horses should be maintained in quarantine and screened for *S. equi* by repeated nasopharyngeal swabs or lavages. This screening should be done in accordance with the protocol outlined for the control of outbreaks (i.e., three samples taken at weekly intervals), with samples tested for *S. equi* by culture and PCR and those animals testing positive being retained in isolation for further investigation and treatment. High standards of hygiene also must always be maintained to prevent indirect transmission between quarantined and resident horses.

No widely available strangles vaccines that are generally accepted as being effective exist. Although strangles occurs in most countries around the world, relatively few

nations currently use vaccination as a means of control or prevention, and in those areas where it is used, strangles remains an endemic and extremely significant equine infectious disease. Despite some limited scientific evidence that strangles vaccines are effective in reducing the severity of disease, their protective immunity is generally poor and short-lived. Importantly, in addition to their limited effectiveness, many problems have been encountered with both local and systemic reactions to strangles vaccines.

Although the original heat-inactivated whole-culture vaccines (so-called bacterins) have higher rates of reaction than the later protein-rich extract products, both have been associated with an unacceptably high level of adverse effects. Recently a live intranasal vaccine based on an apparently avirulent, naturally occurring strain of *S. equi* has been available in North America. Although this type of vaccine—if it remains truly avirulent—might have immunizing and minimal side effects superior to the intramuscularly administered inactivated or protein-based vaccines, problems have also been reported with adverse reactions to this live mutant vaccine strain of *S. equi*. Reactions similar to those signs seen in the natural disease have been reported, albeit at a lower rate than encountered with disease. Such signs include nasal discharge, abscessation of lymph nodes and other sites, allergic reactions, systemic responses, and purpura-like signs. These reactions and the occurrence of *S. equi* abscesses at the site of intramuscular (IM) injection given immediately after intranasal administration of this vaccine demonstrate the potential of this product to produce strangleslike signs in horses.

In keeping with other streptococcal pathogens, the virulence of *S. equi* is most probably determined by a complex series of multiple, genetically coded determinants—best demonstrated by the lack of efficacy of M-protein vaccines and the ability of a live intranasal vaccine strain, the M-protein gene deletion mutants, and heat-inactivated bacterin vaccines to all produce abscesses. Therefore to produce a truly effective strangles vaccine with maximal efficacy and minimal side effects, knowledge and understanding of the mechanisms of the vast majority—if not all—of these determinants are necessary.

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CHAPTER 2.11

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# Equine Protozoal Myeloencephalitis

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In 1962 *segmental myelitis* of horses in central Kentucky was first reported. A similar syndrome, known as *bambeira*, had been recognized in Brazil since the early 1950s. By 1970 the disease had been renamed *focal encephalitis-myelitis*, in recognition of the potential for lesions in any part of the central nervous system (CNS). Replicative protozoal forms (schizonts and merozoites), were seen in association with characteristic lesions, and the syndrome was named *equine protozoal myeloencephalitis* (EPM).

By 1991 the organism had been isolated and propagated in tissue culture and given the name *Sarcocystis neurona*. At this time, EPM had been found in most of the contiguous states of the United States, in southern Canada, and in many countries of Central and South America. Possible cases of EPM in horses native to France have recently been reported. *S. neurona* appears to be the usual causative agent; however, a related organism, *Neospora hughesi*, has caused a scattering of cases. Over recent years, important advances have been made both in understanding the life cycle of *S. neurona* and in identification of risk factors for *S. neurona* infection and EPM. Important challenges remain in improving the diagnosis of EPM and in finding ways to prevent it.

## LIFE CYCLE

The Virginia opossum (*Didelphis virginiana*) is the only definitive host for *S. neurona* in the United States. A closely related opossum, *Didelphis albiventris* (the “white-eared” opossum), carries *S. neurona* in South America. Eating the sarcocyst-infected skeletal muscle of intermediate hosts infects opossums. Ingesting infective sporocysts that have been passed with feces from infected opossums in turn infects intermediate hosts and horses. Recently, a “natural” intermediate host has been discovered—the 9-banded armadillo (*Dasypus novemcinctus*). In addition, the life cycle has been completed experimentally in the striped skunk (*Mephitis mephitis*), Northern raccoon (*Procyon lotor*), and domestic cat. Preliminary evidence suggests that these experimental hosts also can act as natural intermediate hosts. The combined geographic ranges of these hosts cover most of the areas in which EPM occurs. *S. neurona* is clearly quite indiscriminate with respect to its use of intermediate hosts, and others are likely to be found in the near future.

The natural hosts of *N. hughesi* have not been identi-

fied. The closely related *Neospora caninum* uses dogs and cattle as definitive and intermediate hosts, respectively, but evidence to date does not support a role for the dog as definitive host for *N. hughesi*.

## EPIDEMIOLOGY

Only in recent years have reliable data been collected on infection rates of *S. neurona* (and, to a lesser extent, *N. hughesi*) among American horses. Point “exposure” rates have been determined by serum immunoblot testing for *S. neurona*-specific antibody. In this context, exposure indicates current or recent infection. In general, regions with a substantial number of cases among native horses have 26% to 60% seroprevalence rates. Surprisingly, the incidence of new cases of EPM in the United States in 1997 was only 0.14% and ranged among different geographic regions from 0.06% (southern states) to 0.43% (central states) and according to use from 0.01% (farm/ranch) to 0.51% (showing/competition). Horses that are resident at racetracks were not included in this study. Horses, although apparently readily infected with *S. neurona*, are evidently naturally quite resistant to the development of EPM.

Two studies retrospectively have determined risk factors for the development of EPM. Importantly, increased disease risk is associated with age (1-5 and >13 years), season (lowest in winter and increasing with ambient temperature), the presence of opossums, the use of nonsurface drinking water systems, and failure to protect feed from wildlife. Adverse health events—including pregnancy, lactation, lameness, long-distance transportation, even if these occurred many months before onset of disease—also presented an increased risk for the development of EPM.

## CLINICAL SIGNS

Because *S. neurona* organisms can proliferate in any part of the CNS of the horse, an almost infinite variety of clinical syndromes is possible. Signs of the disease usually develop insidiously, but sudden onset also is possible. Clinical experience suggests that most presentations reflect spinal cord involvement; less than 5% of affected horses show signs of brain disease. With the exception of neurologic signs, no other abnormal clinical signs are associated with EPM. Untreated, the disease usually progresses over hours to years; however, signs may remain stable or wax and wane over long periods.



## Signs of Spinal Cord Disease

Often, the histories of horses subsequently found to have EPM are long (months to years) and confusing. Racehorses with EPM often have histories of chronic pelvic limb lamenesses that have failed to respond to therapy for disorders of the hock and/or stifle. Because of quadricep weakness, some of these horses may have intermittent locking of the patella on one or both sides, a sign often attributed to primary musculoskeletal disease. Similarly, back soreness is often reported, presumably a result of unusual stresses put on the muscles of the back and rump by imprecise and uneven gaits. In some cases, the disease has progressed sufficiently for the signs to be unmistakably neurologic. The rider may detect instability on turns, and the horse may have difficulty in making lead changes. A common problem reported among harness horses with EPM is that the affected horse increasingly leans on the outside shaft of the sulky or breaks stride frequently when worked or raced. In other pleasure and performance horses, signs include difficulty in breaking the horse to ride, occasional stumbling or interference between limbs, problems with lead changes, and cross-cantering. In rare instances, there is acute onset of “dog-sitting,” collapse in the thoracic limbs, or recumbency.

Careful neurologic examination of such horses reveals signs of weakness and ataxia of the limbs and trunk. The pelvic limbs are most commonly involved, but any or all of the limbs may be affected. In at least half the cases, signs are more obvious on one side than on the other. During examination of the horse at rest, limb weakness may be evident as exaggerated buckling and/or wobbling of the pelvic limbs when a hemostat or similar tool is run along the skin over the muscles of the back, from withers to tail. In such cases, pressure applied dorsally over the rump or withers may cause buckling of the pelvic or, more rarely, thoracic limbs. When the spinal cord is damaged at the level of the lumbosacral nerve supply to the pelvic limbs (L3-S2 spinal cord segments), the standing horse may be moved sideways by pulling on the tail. Healthy horses or horses with lesions elsewhere in the CNS are extremely resistant to this maneuver. Weakness of a thoracic limb may be evident as buckling of the leg or excessive leaning of the trunk when the horse is forced to hop sideways on the leg while the other is held up. Affected horses also may posture abnormally, with pelvic or thoracic limbs splayed apart or placed abnormally close together. Some veterinarians prefer to formally test these changes in conscious proprioception by placing the limbs in different positions and observing the rate of recovery to a normal stance.

When a horse with EPM is led at the walk on a hard surface and is examined from the side, toe scuffing, asymmetry of stride length, and limb stiffness or, more rarely, hyperflexion may be observed. Occasionally, a lateral, 2-beat “pacing” gait can be observed. Signs such as excessive side-to-side rocking; swiveling; rotation or deviation (“crabbing”) of the pelvis and trunk to one side; or unusually wide, narrow, or inconsistent tracking of the pelvic limbs can best be appreciated when the examiner is behind the horse as it walks. Elevating the horse’s head or walking the horse up and down an incline exacerbates some of these signs. Weakness of the pelvic limbs is evi-

dent as lack of resistance to pressure exerted by pulling sideways with the tail while the horse is walking. During backing, excessive toe dragging, pacing limb movement, or general awkwardness further indicates weakness and incoordination of limbs.

When a horse with EPM is walked forward in small circles—preferably with the circumference of the circle constantly changing—the foot of the outer pelvic limb may describe an arc that is wider than usual (circumduction), which suggests abnormal proprioception. Similarly, the outside foot is more likely to scuff the ground when the horse is walked in circles. When the horse is forced to turn sideways in tight circles (often called the *pivot test*), additional abnormalities may be seen. Horses that are weak and ataxic in the pelvic limbs initially sag backward and then pivot around one or both feet instead of stepping around laterally. Interference between the front feet during this pivot test is another sign of abnormal proprioception.

Approximately 5% to 10% of horses with EPM have some evidence of severe, neurogenic atrophy of muscles of the limbs and trunk. The gluteal muscles, extensors of the stifle (quadriceps, extensor fascia lata, and biceps femoris), and longissimus muscles commonly are affected. Abnormalities of long spinal reflexes in horses with EPM help localize a lesion or lesions. An absent slap test result indicates that damage may lie somewhere between the middle thoracic spinal cord segments and the caudal brainstem. In a healthy horse, slapping behind the shoulder on the opposite side induces visible movement of the muscular process of the arytenoid cartilage of the larynx. A depressed cervicofacial response suggests the presence of a lesion at the corresponding level of the cervical spinal cord. Loss of the cutaneous trunci (“panniculus”) reflex indicates spinal cord damage at the segment bounding the front of the abnormal part of the reflex. Additional useful reflex tests can be performed on the limbs of recumbent animals.

In addition to the signs mentioned previously, unusual signs of spinal cord disease that have been caused by EPM include cauda equina syndrome (that is, paralysis of the bladder, rectum, anus, and penis; sensory loss of the tail and perineum; regional sweating; and sensory loss over a skin segment) and syndromes resembling radial nerve paralysis, sweeney, or stringhalt.

Signs seen at gaits above the walk generally are similar to those described previously in the section on history. It is not uncommon to find actual musculoskeletal injuries and/or lameness that may have developed secondary to imprecise use of the limbs at speed.

## Signs of Brain Disease

Three manifestations of brain disease associated with EPM are acute asymmetric brainstem disease, insidious onset atrophy of the lingual or masticatory muscles, and cerebral syndromes. Acute onset brainstem disease commonly involves signs of cranial nerves VIII (vestibular) and VII (facial) dysfunction. Thus the horse may have facial paralysis and signs of vestibular disease—including staggering gait, abnormal nystagmus and eye positions, poll rotation, head and neck deviation, and a tendency to turn in circles in one direction, usually toward the side of the lesion. Other cranial nerve nuclei or endings can be affected, thus

causing any or all of the following signs: dysphagia (IX, X, XII), stridor (IX, X, XII), tongue weakness (XII), facial hypalgesia (Vs), or weakness of masticatory muscles (Vm). EPM that involves these sites usually is characterized also by mental depression and limb weakness because of collateral damage to structures that stimulate the cerebrum or control motor activity of the limbs, respectively. Unilateral atrophy of masticatory or lingual muscles appears as a singular sign in some horses. Although atrophy of affected muscles is complete and permanent, the disease usually does not progress and has no other abnormal neurologic signs. Cerebral lesions of EPM may affect visual or sensory centers, thus causing blindness—often appreciated as absent menace response—or facial hypalgesia on the side of the face *opposite* the lesion. Touching the nasal septum best tests facial hypalgesia. Other signs of cerebral disease seen in horses with EPM include seizures, mental depression, and demented behavior, such as compulsive walking, fear, rage, or head-pressing in a corner.

## DIAGNOSTIC RULE-OUTS

Spinal cord forms of EPM may appear similar to cervical stenotic myelopathy (CSM, or “wobbles”), spinal cord trauma, equine degenerative myeloencephalopathy (EDM), equine herpesvirus (EHV)-1 myeloencephalopathy, equine motor neuron disease, infectious meningomyelitis (especially that caused by West Nile virus), other diseases that cause spinal cord compression (e.g., extradural tumors, abscesses, degenerating intervertebral disks), causes of focal spinal cord damage (migrating parasite, spinal cord neoplasia, vascular malformation), neuritis of the cauda equina, or congenital conditions (e.g., myelodysplasia). Signs caused by orthopedic problems, peripheral neuropathies, or myopathies (e.g., polysaccharide storage disease) can be confused with EPM.

Numerous differential diagnoses for brain disease caused by EPM exist. Temporohyoid osteoarthropathy, head trauma, lightning strike, infectious meningoencephalitis, aberrant parasite migration, extradural tumor or abscess, and polyneuritis equi all must be considered for the brainstem syndrome. Other causes of cerebral disorders include leukoencephalomalacia, hepatoencephalopathy, hyperammonemia, idiopathic epilepsy, cholesterol granuloma of the choroid plexus, hydrocephalus, tumor, or abscess.

## DIAGNOSIS

Consistent, accurate diagnosis depends on observation of compatible clinical signs interpreted in the context of a tangle of relevant but nondefinitive data. The diagnostician thus must evaluate the case in light not only of clinical signs but also in consideration of history, signalment, clinical progression, response to treatment, geographic location, laboratory and other diagnostic aids, and, most importantly, exclusion of other diseases.

## Clinical Signs

A horse older than 1 year of age that has neurologic signs that are asymmetric and attributable to more than one fo-

cus of CNS disease (e.g., thoracic limb ataxia plus severe atrophy of the gluteal muscles on one side) most likely has EPM. Unfortunately, the majority of cases do not have this “classic” presentation, and the principle of exclusion of other possible diseases becomes paramount. For example, EPM commonly presents in young horses identical to CSM, with symmetric involvement of all four limbs, worse in the pelvic limbs than in the thoracic. In these cases, evaluating the possibility of CSM with high-quality plain radiographs of the cervical vertebrae, with confirmation by contrast myelography as necessary, is vital.

Recently, the principal differential diagnostic challenge in some parts of the country has been West Nile viral encephalomyelitis (WNVE; see Chapter 2.5: “Viral Encephalitis”). Horses with this disease have tremendously varied clinical presentations, often not involving an initial fever. Although fasciculation of the muzzle is the classic sign of WNVE, some affected horses do not show this sign but have acute onset of asymmetric ataxia and weakness of the limbs, sometimes complicated by signs of cranial nerve dysfunction. To differentiate EPM and WNVE, the clinician must be guided by diagnostic aids (as described in the following text) as well as by vaccination history. For brain forms of EPM, caudal brainstem or cranial nerve trauma—either direct, or secondary to temporohyoid osteoarthropathy—is an important differential. High-quality radiography—particularly good-quality dorsoventral views of the skull, supplemented in some cases by computed tomography (CT) or magnetic resonance imaging (MRI) and guttural pouch endoscopy—are required to rule out this possibility.

## Laboratory Aids

Laboratory aids can in no case clinch a definitive *ante mortem* diagnosis of EPM. The usefulness of such tests generally falls into three categories: (1) positive immunoblot for *S. neurona* antibodies, which directly supports the diagnosis; (2) negative immunoblot, which directly tends to exclude the diagnosis; and (3) tests that support alternative diagnoses, thus indirectly excluding the diagnosis of EPM.

### Immunoblots

Serum and cerebrospinal fluid (CSF) immunoblots for *S. neurona* antibodies are almost always positive in horses that have EPM (i.e., because of high sensitivity). Unfortunately, they also frequently are positive in horses that do not have EPM (i.e., because of poor specificity). Obviously, the latter is most problematic in serum immunoblots, but specificity of CSF also is probably no better than 70% in horses with signs compatible with EPM. The reasons for this are several and include the following:

1. Contamination of CSF by blood at the time of collection
2. Contamination of CSF by serum proteins before collection because of “leakiness” of the blood-brain barrier
3. Laboratory error

This author’s recent survey of the three different laboratories that perform this test suggests that this last issue

may be more important than generally was recognized. Two calculated indices, the albumin quotient and the immunoglobulin G (IgG) index, have been advanced as indicators of CSF contamination and intra-CNS antibody production, respectively. Close theoretic and experimental analyses suggest that they do neither task very well and probably are not worth the expense or headaches associated with interpretation. The Relative Quantity (RQ) CSF value (Neogen, Inc., Lexington, Ky.) offers a way to quantify the antibody response to *S. neurona* as a unitless value between 5 and 100. High values are presumably more supportive of a diagnosis than are lower values. In addition, the value should decline during successful response to treatment. In summary, in a clean CSF sample from a horse that has normal CSF cytology and red blood cell (RBC) count of less than 50/ $\mu$ l, a positive immunoblot is consistent with a diagnosis of EPM but does not prove it. In contrast, a negative serum or CSF immunoblot result predicts with a high degree of certainty that a horse does not have EPM.

#### **Cerebrospinal Fluid Analysis**

Most horses with EPM have normal CSF cytology. About 5% of all cases have abnormalities, including modest elevations of protein (usually <120 mg/dl) and cell (usually <50 cells/ $\mu$ l) concentration. Dramatically high cell concentrations (>1000 cells/ $\mu$ l) are more supportive of bacterial meningitis, whereas intermediate concentrations suggest acute viral disease. The use of CSF cytology has been particularly important in attempts to distinguish EPM from WNVE. In the latter case, counts frequently are 20 to 150 cells/ $\mu$ l, with predominantly mononuclear differential. In a few diseases, CSF cytology can be diagnostic. Examples include the xanthochromia, high protein concentration, and normal cell count that characterize EHV-1 myeloencephalopathy or the finding of tumor cells in some cases of metastatic melanoma or lymphoma. In situations in which WNVE is an alternative diagnosis, this test should always be performed.

#### **Serology**

Serologic evidence of infection with another agent capable of causing CNS signs can tend to exclude the diagnosis of EPM. Examples include high (single) or rising (paired) titers of serum neutralization (SN) antibodies against EHV-1, IgM-capture (MAC)-ELISA titers greater than 1:400, and plaque-reduction neutralization (PRNT) titers of greater than 1:100 against eastern equine encephalitis (EEE) or WNVE viruses. Initial indications are that, as is the case with vaccination and EEE, horses vaccinated against WNVE remain MAC-ELISA-negative; thus a positive result with this test even on a single blood sample highly supports a diagnosis of WNVE infection and, by inference, WNVE.

#### **Other Blood Tests**

A modest elevation of serum creatine kinase (CK) activity can suggest a diagnosis of equine motor neuron disease (EMND) in a horse with limb weakness, whereas a very high CK activity ( $10^4$ - $10^6$  IU/L) indicates that myopathy likely is responsible for the clinical signs seen. A low  $\alpha$ -tocopherol (vitamin E) concentration (<1.5  $\mu$ g/ml) may suggest the possibility of either EDM or EMND.

### **Response to Equine Protozoal Myeloencephalitis Treatment**

About three quarters of the improvement seen in horses treated for EPM occurs within 30 days of beginning therapy; thus treatment response is a legitimate method of retrospectively inferring the diagnosis. As always, there are caveats; some horses with CNS disease (WNVE being a particularly good example) improve with time and no treatment. Conversely, some horses with EPM either do not improve or worsen while on appropriate treatment for EPM. Both results would lead to incorrect inferences as to cause of the problem.

#### **Other Diagnostic Aids**

Electromyography, electroencephalography, and biopsies of muscle or peripheral nerves all can be useful in classifying signs precisely or in incriminating diseases other than EPM. Alternative diagnostic techniques (including acupuncture) are of unproved value or are, in this author's experience, of no value or negative value.

### **TREATMENT**

The cornerstone of therapy for EPM undoubtedly is the use of appropriate antimicrobial drugs. Ancillary use of antiinflammatory, antioxidant, biologic response modifiers, and physical therapy is indicated in some cases.

#### **Antiprotozoal Drugs**

The standard therapy for EPM for nearly 30 years has been combination of a sulfonamide with pyrimethamine. These drugs affect successive steps in protozoal folate synthesis. Originally, combinations of pyrimethamine tablets with trimethoprim-sulfonamide tablets were used. To make treatment more affordable, many compounding pharmacies have for the last several years produced premixed sulfadiazine-pyrimethamine solutions/suspensions (usually 17 mg pyrimethamine/ml and 333 mg sulfadiazine/ml). Although no comparative data for these compounded drugs exist, they seem to work as well as the more expensive tablets. In general, the dosage used is 20 mg sulfadiazine/kg plus 1 mg pyrimethamine/kg (usually 30 ml of suspension or paste) given once daily by syringe into the mouth. Hay should not be fed for at least an hour before or after medication because it may interfere with the absorption of pyrimethamine. Usually a double dose of compounded drug is given during the first week to rapidly establish effective CNS concentrations.

The duration of treatment is somewhat arbitrary; however, the University of Florida researchers recommend a standard course of therapy of 6 months in all cases, except in those in which toxic side effects are an issue. Even if complete resolution of signs is seen within this period, completion of the full course may minimize the chance of relapse. Toxic effects of long-term therapy include anemia (usually >20% packed cell volume [PCV]), leukopenia (sometimes with glossitis and oral ulcerations), abortion, and birth (from treated mares) of foals with lethal bone marrow and renal dysplasias. Toxic side effects are minimized by the provision of feedstuffs high in natural (reduced) folate. Examples include alfalfa hay, pasture,

and Brewer's yeast. Synthetic folic acid is probably not useful in this setting, and experimental evidence from other species suggests that it may even interfere with absorption of natural folate.

Ponazuril (toltrazuril sulfone) is the only product currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of EPM. It is a broad-spectrum anticoccidial drug that acts principally on the plastid body organelle, a vestigial remnant of a unicellular plant structure. The drug is marketed as dial-by-weight syringes that contain sufficient product for a 28-day course of 5 mg/kg/day for a 500-kg horse. Studies so far suggest that when used as directed, the drug has virtually no adverse side effects. Because of some concerns about relapse after initial improvement, some practitioners recommend a second course of ponazuril after the initial one.

Data from laboratory animals suggest the potential for synergism between ponazuril and pyrimethamine. For this reason, some rationale exists for the use of standard sulfadiazine/pyrimethamine therapy concurrent with ponazuril as a combination therapy. Each should be given according to the guidelines discussed previously.

Forms of diclazuril and toltrazuril marketed for non-equine species previously could be imported from Canada and used off-label for the treatment of EPM. The treatment niche of these drugs has been filled by the closely related ponazuril, and they no longer can legally be imported. A pelleted form of diclazuril, applied as a top-dressing, has been evaluated in preparation for application to the FDA for approval for use as an EPM treatment. Nitazoxanide (NTZ), another product with broad antiprotozoal activity, also has been evaluated clinically and is in the FDA review process. Neither product is available for veterinary use. Various tetracycline derivatives, including oxytetracycline (given intravenously) and doxycycline (given orally) have been tried as treatments for EPM. These drugs have some activity against *Sarcocystis* spp., but no data are available on their effectiveness in the treatment of EPM.

The comparative effectiveness of different treatments is not known because of the different conditions prevailing in the few studies done on individual drugs. No comparative studies have been done. The impression of many clinicians is that the two treatments currently available have similar efficacy. Overall, approximately 60% to 70% of horses with EPM improve with therapy, and 15% to 25% recover completely. An inverse relationship appears to exist between the time taken to initiate treatment after the onset of signs and the clinical outcome. Regardless of the type and duration of therapy, most improvement is seen during the first month, although further improvement can occur for months to years afterward.

### Ancillary Therapies

Nonsteroidal antiinflammatory drugs (NSAIDs) such as flunixin meglumine often are given to moderately or severely affected horses with EPM during the first 3 to 7 days of antiprotozoal therapy. For horses in danger of falling down or that exhibit signs of brain involvement, the additional use of corticosteroids (0.05 mg/kg dexamethasone q12h) and dimethyl sulfoxide (1 g/kg as a 10% solution

IV or by nasogastric tube q12h) for the first several days may control the inflammatory response and associated clinical signs and provide time for the antiprotozoal drugs to begin to work.

Because the damaged CNS is susceptible to oxidant injury, it has become common practice to use pharmacologic doses of the antioxidant vitamin E (e.g., 20 IU/kg daily PO) throughout the period in which horses are treated for EPM. Although vitamin E therapy may not significantly alter the course of recovery, it is considered unlikely to do any harm. Based on the assumption that horses that develop EPM may, in some respect, be immune-compromised, immunomodulators sometimes have been included in treatment of the disease. The drugs used include levamisole (1 mg/kg PO q12h for the first 2 weeks of antiprotozoal therapy and for the first week of each month thereafter), killed *Propionibacterium acnes* (EqStim), and mycobacterial wall extract (Equimune IV). The recently licensed EPM vaccine is being used "off-label" for the same purpose. No study has been performed to date to evaluate the efficacy of any of these adjuvant treatments.

### Treatment Relapses

Horses that revert after treatment to negative status on CSF immunoblot appear to be at little or no risk for relapse. Unfortunately, only about 20% of horses become negative within 6 months of beginning therapy. Among those horses that remain positive, there appears to be a significant (10%-20%) threat of clinical relapse within the 2 years after therapy is discontinued. This finding holds true regardless of the completeness of the initial clinical response; thus a follow-up CSF immunoblot evaluation (usually 6 months after therapy is begun) is extremely useful, even without initial immunoblot. Three reasonable approaches to the horse that remains CSF-positive are as follows:

1. Continue therapy with either or both of the principal treatments described previously.
2. Discontinue all therapy.

OR

3. Switch to intermittent therapy.

One plan used for horses treated at the University of Florida is sulfadiazine/pyrimethamine for 2 days (i.e., weekends) per week. Follow-up CSF immunoblots should be performed every 6 months, at which time a new 6-month plan can be determined.

Because adverse health events, such as other diseases, long-distance transportation, and heavy athletic use have been shown to predispose horses to the development of EPM, CSF-positive horses around such events, to the extent that it is practicable, should be treated. For example, a horse might be treated a week before and after long-distance transportation.

### PREVENTION

Horses presumably ingest infective opossum sporocysts with feed or water. Opossums are omnivores and are attracted to grains, moist or dry cat or dog food, fruit, or

garbage. Therefore horse feed and pet food should not be left out; open feed bags and garbage should be kept in closed galvanized metal containers; bird-feeders should be eliminated; and fallen fruit should be removed. Opossums can be trapped and relocated. Less practically, paddocks can be opossum-proofed by placing a partially buried 2-inch  $\times$  4-inch mesh fence and electric wire on the outside of existing horse fence. Sporocysts probably are distributed from the point of deposition by birds and/or insects, so it may be prudent to control populations of these potential vectors, at least within horse barns. An issue that has not been addressed is the possibility of contamination of commercially prepared feeds with *S. neurona* sporocysts. Because they have been heated (60°-166° C) during preparation, "hot-processed" feeds (e.g., steam-flaked, pelleted, or extruded feeds) are unlikely to harbor viable sporocysts. Further work must be performed to confirm that cold-processed commercial supplies are sporocyst-free.

Intermediate hosts (armadillo, skunk, etc.) cannot directly infect horses with *S. neurona*. They only serve to perpetuate the life cycle by infecting the opossum. Attempts to control these hosts on an operations level is likely to have minimal effect on contamination of the premises with *S. neurona*. In this respect, elimination of cats may be a particularly fruitless exercise, in light of their apparent low prevalence of *S. neurona* infection.

As outlined previously, drugs used to treat EPM may have applications as preventive agents, much in the way they are used to prevent coccidiosis in chickens and pigs. Ponazuril and diclazuril are currently being investigated

for this purpose in horses, and some form of daily or other intermittent preventive product likely will be available within the next several years.

Fort Dodge Animal Health in Overland Park, Kan., currently is selling an EPM vaccine under limited license. The vaccine, which comprises killed cultured whole organisms in proprietary adjuvant, is of unknown efficacy because EPM cannot reliably be produced experimentally in the horse. The vaccine has been shown to induce both protozoacidal antibodies and specific cell-mediated responses in experimental horses. A 3-year case-control study to evaluate efficacy is now under way; probably results will not be available for several years. The vaccine has been shown to be safe but may cause spurious positive immunoblot results, especially when the vaccine is given to horses that are already immunoblot-positive in serum.

### Supplemental Readings

Dubey JP, Lindsay DS, Saville WJ et al: A review of *Sarcocystis neurona* and equine protozoal myeloencephalitis (EPM). *Vet Parasitol* 2001; 95:89-131.

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## CHAPTER 2.12

# Equine Monocytic Ehrlichiosis

MAUREEN T. LONG

Gainesville, Florida

An acute, fulminate colitis of horses was first recognized and described in the Potomac River area in the mid 1970s. *Neorickettsia risticii* (formerly known as *Ehrlichia risticii*) was isolated and identified in 1984 as the causative agent of this syndrome, which was named *equine monocytic ehrlichiosis* (EME), or *Potomac Horse Fever*. Serologic surveys indicate that the disease is widespread and occurs in the United States, Canada, and Europe. Three clinical syndromes of EME are recognized, and these include varying degrees of overt clinical illness characterized by infectious typhlocolitis, subclinical infection, and 7-month abortion. The most important recent contribution to understanding of this disease is information gained toward completion of the life cycle of *N. risticii*.

### BIOLOGY, LIFE CYCLE, AND EPIDEMIOLOGY

*N. risticii* belongs to a group of organisms called the *purple bacteria* and is a tiny gram-negative organism that exhibits a high degree of pleomorphism. Like ehrlichial organisms, this microorganism stains a blue to purple color with Romanowsky's stain, has a host-cell predilection for leukocytes, and depends on a vector for transmission. This organism is unique in its propensity for enterocytes of the equine intestine. On electron microscopy, this organism resides in the cytoplasm of infected cells within host-cell-lined vacuoles (morulae). The organisms can be seen singly or in groups, the former being 0.8 to 15  $\mu$ m electron-lucent and the latter 0.2 to 0.4  $\mu$ m electron-dense.

garbage. Therefore horse feed and pet food should not be left out; open feed bags and garbage should be kept in closed galvanized metal containers; bird-feeders should be eliminated; and fallen fruit should be removed. Opossums can be trapped and relocated. Less practically, paddocks can be opossum-proofed by placing a partially buried 2-inch  $\times$  4-inch mesh fence and electric wire on the outside of existing horse fence. Sporocysts probably are distributed from the point of deposition by birds and/or insects, so it may be prudent to control populations of these potential vectors, at least within horse barns. An issue that has not been addressed is the possibility of contamination of commercially prepared feeds with *S. neurona* sporocysts. Because they have been heated (60°-166° C) during preparation, "hot-processed" feeds (e.g., steam-flaked, pelleted, or extruded feeds) are unlikely to harbor viable sporocysts. Further work must be performed to confirm that cold-processed commercial supplies are sporocyst-free.

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*N. risticii* belongs to a group of organisms called the *purple bacteria* and is a tiny gram-negative organism that exhibits a high degree of pleomorphism. Like ehrlichial organisms, this microorganism stains a blue to purple color with Romanowsky's stain, has a host-cell predilection for leukocytes, and depends on a vector for transmission. This organism is unique in its propensity for enterocytes of the equine intestine. On electron microscopy, this organism resides in the cytoplasm of infected cells within host-cell-lined vacuoles (morulae). The organisms can be seen singly or in groups, the former being 0.8 to 15  $\mu$ m electron-lucent and the latter 0.2 to 0.4  $\mu$ m electron-dense.

bodies. Original observations of this organism presupposed a life cycle similar to ehrlichial organisms that depend primarily on ticks for transmission.

Completion of the life cycle of *N. risticii* has been the goal of intense effort that has spanned almost 20 years, with early efforts to identify a tick vector and overwintering reservoir hosts proving unrewarding. Important observations regarding the biology of *N. risticii* contributed to the recent gains toward completion of its life cycle. First, sequencing of the 16S rRNA gene demonstrated that the different *Ehrlichia* species aligned according to three separate genogroups and that *N. risticii* has the highest degree of homology to *Ehrlichia sennetsu* (human monocytic ehrlichiosis; now known as *Neorickettsia sennetsu*) and *Neorickettsia helminthoeca* (salmon poisoning of dogs). Both host species, human and dogs, are infected via ingestion of raw fish infected with metacercaria stages of flukes that contain these bacteria. Finally, oral transmission of *N. risticii* was demonstrated by experimental feeding of *N. risticii* itself and in feces that contained *N. risticii* to ponies. Because all previous attempts at tick transmission were unrewarding, detection and transmission studies with mollusk reservoir hosts were pursued.

Evidence to date indicates that a possible vector of *N. risticii* is a virgulate trematode of freshwater snails. The metacercaria stage of these trematodes also infects many aquatic insects. How the agent is actually transmitted from snails or aquatic insects to horses is unknown. Thus far, trematode stages (cercaria and sporocysts) of flukes that infect the snail *Juga yrekaensis* and are inoculated intravenously and subcutaneously into horses can successfully transmit the EME agent. The snail species *Elimia livescens*, found in Ohio, is also infected with *N. risticii*. Although the metacercariae of these helminths can theoretically penetrate skin, *J. yrekaensis* secretions did not transmit intradermally to horses that were standing in water containing metacercariae. However, oral ingestion of the aquatic caddisfly insect *Dicosmoecus gilvipes* that was infected with the metacercaria resulted in transmission of EME to one horse. The metacercariae of these flukes have a broad host range, and other metacercariae-infected aquatic insects that harbor *N. risticii* DNA include species of caddisflies, mayflies, damselflies, dragonflies, and stoneflies.

Although documentation of *N. risticii* infection is widespread, the highest seroprevalence and occurrence of disease is associated with endemic areas. The highest seroprevalence within endemic areas is usually located near freshwater streams and rivers. High risk factor of exposure to *N. risticii* is correlated with proximity to ponds, time outside, and reduced insecticide use. In addition, the occurrence of *N. risticii* is highly seasonal in temperate climates, with the highest onset of clinical signs occurring in midsummer to late summer. In endemic areas in California, the highest infection rates of *N. risticii* in *J. yrekaensis* snails are late spring and late summer. In a study in Ohio, *E. livescens* snails were infected primarily between June and October. The highest biting activity of caddisflies is also midsummer to late summer.

## CLINICAL SIGNS

Seroepidemiologic surveys reveal a higher prevalence of exposure to *N. risticii* than that which can be accounted for

by overt clinical disease alone. Evidence is overwhelming that the majority of clinical disease appears to be mild or subclinical. Subclinical infection is seasonal in occurrence; increases in antibody titers occur in healthy horses in late summer and early fall. July and August have the highest seroprevalence.

Overt clinical illness attributed to *N. risticii* is characterized sudden onset of anorexia, depression, and a biphasic increase in body temperature. The first increase in body temperature occurs approximately 7 to 10 days after experimental infection. These early elevations in body temperature are usually mild, between 38.8° C and 39.3° and are often transient, lasting 1 to 2 days. The second febrile episode, which occurs 10 to 14 days after experimental infection, is usually more severe and lasts 5 to 10 days. During this second episode of pyrexia the other common clinical signs usually occur. Anorexia is one of the most common features of EME and can be profound. The degree of anorexia is independent of the severity of other clinical signs, such as diarrhea and fever. Fecal consistency in clinically ill horses varies from no detectable change in stool to severe, watery, and protracted diarrhea. Abdominal pain can accompany gastrointestinal (GI) signs and is usually associated with the development of severe diarrhea. Rarely, horses can have nasogastric reflux secondary to severe ileus. Another consistent feature of EME is the lack of intestinal sounds in both paralumbar fossae and a large area of hyperresonance (ping) in the right paralumbar fossa. Dehydration and endotoxemic-like signs occur and result in cardiovascular compromise characterized by elevations of heart and respiratory rates and congested mucous membranes. The duration of clinical signs in acutely ill horses varies from 2 to 10 days, with the majority persisting for 8 days.

Affected horses are also predisposed to laminitis, the occurrence of which is also independent of the development and severity of diarrhea. Outbreaks of EME characterized by high fever, depression, hypovolemic shock, and very early onset of severe laminitis without significant GI signs have been reported. This specific syndrome is currently attributed to possible strain differences in *N. risticii*. Subcutaneous edema along the ventral abdomen has also been observed in horses with EME.

To date, no evidence exists that *N. risticii* infection results in chronic disease. Although *N. risticii* can be detected by culture and polymerase chain reaction (PCR) during incubation and clinical disease (at least 30 days after inoculation), attempts at experimental isolation after clinical signs have abated have been unsuccessful. Antibody titers remain high for periods greater than 12 months, as though infection may be persistent, but the majority of untreated experimentally infected ponies and horses recover uneventfully. Long-term problems all appear to be related to sequelae such as laminitis. All initial leukon and hematologic abnormalities resolve during the recovery phase; a short-term rebound leukocytosis is the most prominent finding. Infection with *N. risticii* should not be considered a major differential in horses with chronic hematologic abnormalities.

The relationship between infection with *N. risticii* and loss of reproductive performance was first suggested by reproductive abnormalities observed on a farm with a high



incidence of clinical disease attributed to infection with *N. risticii*. Pregnant mares, which exhibit clinical signs of EME, subsequently abort around 7 months of gestation, regardless of the severity of infection. In mares infected at 90 to 120 days of gestation, subsequent abortion occurs at 180 to 240 days of gestation. Abortions are spontaneous, and fetuses are fresh. Mares exhibit few premonitory signs, but retained placenta is common after abortion. Any clinical illness at the time of abortion is usually associated with retained placenta. Severity of earlier clinical illness is independent of the occurrence of abortion.

## CLINICAL PATHOLOGY

Alterations in hematologic parameters include increases in both packed cell volume (PCV) and plasma protein concentration secondary to dehydration and hemoconcentration. A transient nonregenerative anemia may develop and can be profound in some horses. Transient decreases in total white blood cell (WBC) counts are common. The development of an absolute leukopenia is variable; when present, neutropenia, lymphopenia, and eosinopenia can all occur. Peripheral blood monocyte counts can also increase. Horses often present with evidence of tendency to clot, and activation of coagulation has been documented in experimentally and naturally infected horses with EME. Significant abnormalities include significant changes in plasma fibrinogen, fibronectin, factor VIII,  $\alpha_2$ -antiplasmin, and plasminogen. An increasing severity of fibrinogen, factor VIII, and activated partial thromboplastin time (APTT) is correlated with decreased survivability.

## DIAGNOSIS

A combination of clinical lesions, clinicopathologic abnormalities, antibody testing, and antigen detection is required to definitively diagnose infection with *N. risticii ante mortem*. Differential diagnoses include any clinical syndrome of enterocolitis. Specific syndromes include salmonellosis, clostridial diarrhea, intestinal ileus secondary to displacement or obstruction, and equine viral arteritis. Diagnostic tests specific to ruling out these diseases should be concurrently pursued.

Both indirect fluorescent antibody (IFA) and enzyme-linked immunosorbent assay (ELISA) test formats have been developed to detect antibody for *N. risticii*; however, most diagnostic laboratories rely on the IFA. Paired serum titers must be evaluated; single titers are useless for confirmatory testing for EME. A value of 1:80 has been proposed as positive; however, PCR techniques were used to discover that a few naturally infected horses were actually positive in the face of lower titers. Experimentally infected horses experience a large rise in titer between 4 and 10 days into the onset of clinical signs; a fourfold rising titer often can be demonstrated within the first week. The IFA does not differentiate titers that are the result of vaccination or previous infection. A high number of false-positive results also may result from IFA testing. Several ELISA formats have been developed experimentally and have demonstrated enhanced specificity, along with excellent sensitivity in comparison with IFA. Presently none of these ELISA for-

ats is offered commercially. Neither adult nor fetal serology is of any value for diagnosis of *N. risticii* abortion.

Detection of antigen can be performed in three ways: (1) identification of morula within WBCs during the acute phase of the disease, (2) isolation of the organism from WBCs, and (3) PCR of WBCs or feces. During the acute phase of the disease and before administration of antibiotics, peripheral blood smears can be stained with Wright/Giemsa, and purple cytoplasmic inclusions can be visualized within monocytes. This technique is laborious, and if initial leukopenia is profound, infected cells may be difficult to detect. Successful isolation of *N. risticii* from peripheral blood requires cell-culturing capability within the testing laboratory and can take from several days to weeks of culturing before detection is successful.

PCR performed on buffy coat or on feces is a sensitive way to detect *N. risticii* antigens. In experimentally infected animals, PCR performed on feces or buffy coat was more sensitive than was culture. However, PCR has proven somewhat less sensitive than culture for clinical specimens. This slightly decreased sensitivity may be due to specimen handling. Under appropriate specimen handling, PCR offers a sensitive detection technique with minimal delay. Furthermore, in clinical specimens, detection by PCR on blood is more sensitive than detection in feces. This latter finding may also be due to specimen handling and quality, as large numbers of *N. risticii* are shed into bowel lumen in epithelial cells. In untreated horses, *N. risticii* can be detected by PCR for up to 30 days after infection. Comparison of IFA to PCR detection has demonstrated that horses may be PCR-positive even when titers are still low—less than 1:20. Thus testing early during the stage of disease—before treatment—will likely yield positive clinical specimens.

## NECROPSY FINDINGS

No pathognomonic *post mortem* changes for *N. risticii* exist. Gross necropsy findings in the acute stage of disease primarily include a fluid-filled cecum and large colon. Grossly visible areas of necrosis and hyperplasia of lymphoid follicles and lymph nodes also occur. Mucosal hyperemia and ulceration are common findings. Microscopic changes include areas of moderate-to-severe lymphohistiocytic infiltration of the submucosa and lamina propria. In severe cases, mucosal sloughing into the intestinal lumen occurs. Both silver staining and immunohistochemical staining techniques have been described for detection of *N. risticii* in tissues; however, these are not routinely used in the diagnostic laboratory setting. Electron microscopy can be used to detect *N. risticii* infection during disease. Enterocytes of horses have large numbers of inclusions laden with electron-lucent and dense bodies. Macrophages and enterocytes within the intestinal lumen often contain the organism.

Unlike disease in the adult, *post mortem* changes in fetuses aborted due to *N. risticii* are consistent, diagnostic, and unique to this abortion syndrome. Grossly, fetuses have voluminous meconium and soft, friable livers. A triad of histologic pathology is seen—including lymphohistiocytic enterocolitis, periportal hepatitis, and severe splenic inflammation characterized by both intense lymphohisti-



ocytic infiltration and lymphoid necrosis. Fetuses often also have a lymphohistiocytic myocarditis. The enterocolitis is the most remarkable finding and is usually composed of inflammatory infiltrates of lymphocytes, macrophages, and neutrophils. Perivascular inflammation is prominent in the submucosa, and inflammatory cells are often in the intestinal lumen. These changes are seen within both the small and large intestines of aborted fetuses.

## TREATMENT

Tetracyclines still remain the drugs of choice against *N. risticii* infection. Tetracycline should be administered during clinical illness. Similar to other infections, such as *Anaplasma* in cattle and *Ehrlichia* in dogs, treatment of horses during the incubation period delays clinical signs, but illness, albeit somewhat less severe, still may occur. Therefore antibiotic treatment as prophylaxis will likely be unrewarding. Treatment with oxytetracycline (6.6 mg/kg IV q24h for 5 days) in horses that display acute clinical illness due to *N. risticii* results in rapid response to treatment within 24 to 48 hours. Other antibiotics with demonstrated efficacy *in vivo* include a combination of rifampin (10 mg/kg PO q12h) with erythromycin stearate (25 mg/kg PO q12h) for 5 days of therapy. At present, whether treatment of clinically affected broodmares during the diarrheal stage of disease prevents subsequent abortion remains unknown. Anecdotal reports suggest a decreased occurrence of post-EME abortions on farms with high incidences of EME with early institution of antimicrobial therapy.

Supportive therapy that consists of the administration of polyionic intravenous (IV) fluids is extremely important in the treatment of hypovolemia and shock. Diarrhea can be profuse, and many horses develop severe prerenal azotemia that must be corrected by fluid therapy even with early antibiotic therapy. Addition of calcium, magnesium, and potassium to fluids may be necessary in cases of prolonged anorexia. Antiinflammatories that consist of flunixin meglumine (0.25-1.1 mg/kg IV or PO q6-8h) or phenylbutazone (2.2-4.4 mg/kg IV or PO q12h) are indicated. The most common potentially lethal sequela to EME is laminitis. Institution of other preventive therapies can be initiated early. No specific therapy is universally recognized to prevent laminitis, and hard data regarding the efficacy of most of the following therapies is lacking. Addition of sodium heparin (40 to 60 IU/kg SQ q8h) and aspirin (10-20 mg/kg PO every other day) can be administered to prevent microvascular thrombi formation. The use of dimethyl sulfoxide (DMSO) to scavenge hydroxyl radicals (1g/kg as a 10%-20% solution IV or PO q24h) is an additional mode of antiinflammatory therapy. For vasodilatation of microvasculature, parenteral administration of acepromazine (0.02-0.04 mg/kg IM q6-8h) or the applications of nitroglycerin directly to digital circulation are common treatment options.

## PREVENTION

Several vaccines have been marketed for protection against infection with *N. risticii*. These products consist of killed or inactivated bacterins with adjuvant. Few publications that examine the efficacy of vaccination against *N. risticii* exist. One early report demonstrated that although experimentally infected ponies became clinically ill, the severity of clinical illness was significantly less than that of the nonvaccinated ponies. Recent epidemiologic studies have indicated that vaccination outside endemic areas is not cost-effective. Overall, vaccination of horses resulted in little reduction in cost or in severity of illness in comparison with nonvaccinated horses. Anecdotally, veterinarians that practice in endemic areas indicate that vaccinated horses appear to develop less severe disease. However, these findings must be interpreted with caution; simultaneous early intervention with tetracycline and better supportive care are also factors that have affected survivability in EME-vaccinated horses. Vaccine failure or the development of fulminant disease in vaccinated horses has been attributed to antigenic variation between field strains of *N. risticii*. *N. risticii*-induced abortion is not prevented by vaccination.

## CONTROL

The recent work toward completion of the life cycle will offer profound implications for control of EME in endemic areas. Clearly, limiting access of livestock to freshwater streams and ponds is important. At the very least, access should be limited during months of peak incidence. Control of biting or orally ingested vectors as yet to be identified will likely be an important focus for future control methods.

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## CHAPTER 2.13

# Equine Granulocytic Ehrlichiosis

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**E**quine granulocytic ehrlichiosis (EGE) is a seasonal rickettsial disease of horses that was first reported in the late 1960s in the foothills of northern California. The etiologic agent is a member of the *Anaplasma phagocytophila* genogroup, gram-negative cocci with a tropism for granulocytes. Clinical manifestations include fever, partial anorexia, depression, limb edema, petechiation, icterus, ataxia, and reluctance to move. Hematologic changes are thrombocytopenia, elevated plasma icterus index, decreased packed cell volume (PCV), and marked leukopenia that involves first lymphocytes and then granulocytes. Transmission by a tick vector is likely responsible for the seasonal appearance of the disease, which is being diagnosed with increasing frequency in the United States, Canada, Brazil, and northern Europe.

### ETIOLOGIC AGENT

The causative agent of EGE is *Anaplasma phagocytophila* (formerly known as *Ehrlichia equi*). The organisms are found in membrane-lined vacuoles within the cytoplasm of infected eukaryotic host cells, primarily granulocytes. These inclusion bodies consist of one or more coccoid or cocci bacillary organisms approximately 0.2  $\mu\text{m}$  in diameter to large granular structures called *morulae*, which are approximately 5  $\mu\text{m}$  in diameter. Organisms are visible under high, dry, or oil immersion with light microscopy. They stain deep-blue to pale blue-gray with Giemsa or Wright's-Leishman's stains.

The *A. phagocytophila* genogroup includes the agent of tickborne fever of ruminants in Europe (formerly known as *Ehrlichia phagocytophila*) and the recently reported agent of human granulocytic ehrlichiosis (HGE) in the United States and Europe. Members of this genogroup have similar morphology and neutrophil cell tropism and are very closely related serologically and genetically to one another. The DNA sequences of the 16S rRNA gene from the peripheral blood of naturally infected horses in Connecticut and California are identical to that of the HGE agent. Moreover, injection of infective human blood from HGE patients into horses causes typical equine ehrlichiosis, which can be transmitted to other horses. It induces protection in horses to subsequent challenge with *E. equi*. These data suggest that the agent of EGE and HGE are probably conspecific and were at the origin of reclassification of the agents under the name *A. phagocytophila*.

### EPIDEMIOLOGY

The horse represents an aberrant host, and it seems unlikely that infected horses could serve as effective reser-

voirs of *A. phagocytophila* because the presence of the organism in an affected animal is limited to the acute phase of the disease. Horses of any age are susceptible, but the clinical manifestations are less severe in horses younger than 4 years of age. Horses from endemic areas have a higher seroprevalence of antibody to *A. phagocytophila* than do horses from nonendemic areas, which suggests the occurrence of subclinical infection in some animals. Furthermore, horses introduced into an endemic area are more likely to develop EGE than are native horses. Persistence of *A. phagocytophila* has not been demonstrated in naturally or experimentally infected animals. The disease is not contagious, but infection can be transferred readily to susceptible horses with transfusion of as little as 20 ml of blood from horses with active infection. Most often, one infected horse is observed in groups of horses in the same pasture. The disease has been reported in horses in California, Washington, Oregon, New Jersey, New York, Colorado, Illinois, Minnesota, Connecticut, Florida, Wisconsin, and—outside the United States—in Canada, Brazil, and northern Europe.

In recent years, EGE has been experimentally transmitted by the western black-legged tick (*Ixodes pacificus*) and the deer tick (*Ixodes scapularis*). Furthermore, an epidemiologic study in California showed that the spatial and temporal pattern of EGE cases closely paralleled the well-characterized life history and distribution of *I. pacificus* but not of other ticks commonly associated with horses. In the East and Midwest of the United States, *I. scapularis* is the vector of granulocytic ehrlichiosis; small rodents such as white-footed mice, chipmunks, and voles, as well as the white-tailed deer, are potentially important reservoirs. In California, white-footed mice, dusky-footed wood rats, cervids, lizards, and birds have been proposed as reservoirs.

### CLINICAL SIGNS AND HEMATOLOGIC FINDINGS

The prepatent period after experimental exposure of horses to infected ticks is 8 to 12 days and 3 to 10 days after needle inoculation of infectious blood. The inoculation period of the natural infection is believed to be less than 14 days, based on the time of onset of clinical signs in horses that had presumptive exposure to ticks while on a trail ride before returning to a nonendemic area for EGE.

The severity of clinical signs of EGE is a function of age of the horse and the duration of the illness, which can make clinical recognition of EGE difficult at the time of the first examination. Adult horses more than 4 years of age generally develop the characteristic progressive signs—

fever, depression, partial anorexia, limb edema, petechiation, icterus, ataxia, and reluctance to move. Clinically and experimentally, horses less than 4 years old appear to develop milder signs, including moderate fever, depression, moderate limb edema, and ataxia. In horses less than 1 year old, clinical signs may be difficult to recognize, with only a fever present. During the first 1 to 2 days of infection, fever is generally high, fluctuating from 39.4° to 41.3° C (102.9° F to 106.3° F).

Initial clinical signs are reluctance to move, ataxia, depression, and occasionally, icterus and petechiation of nasal septum mucosa. Weakness and ataxia can be severe to the point that horses will sustain fractures after falling. Staggering is seen commonly, and the tendency to assume a base-wide stance leads to the suspicion of proprioceptive deficits. Partial anorexia develops in most cases. Limb edema and more severe signs of disease develop by day 3 to 5, with fever and illness lasting 10 to 14 days in untreated horses. Heart rate is often modestly high (50 to 60 bpm). Cardiac involvement with development of cardiac arrhythmias occurs rarely. Ventricular tachycardia and premature ventricular contractions have been observed with the usually recognized clinical signs. The clinical course of the disease ranges from 3 to 16 days. The disease is normally self-limiting in untreated horses; fatalities can occur due to secondary infection and to injury secondary to trauma caused by incoordination. Abortion has not been observed in pregnant mares, nor has laminitis been a reported feature of the clinical syndrome.

The initial stage of the disease is characterized by the development of a fever and may be mistaken for a viral infection. The differential diagnosis for EGE includes purpura hemorrhagica, liver disease, equine infectious anemia, equine viral arteritis, and encephalitis.

Laboratory abnormalities in horses affected with EGE consist of leukopenia, thrombocytopenia, anemia, icterus, and characteristic inclusion bodies (morulae) in neutrophils and eosinophils. The morulae are pleomorphic and blue-gray to dark-blue in color and often have a spoke-wheel appearance.

## **PATHOLOGY**

The characteristic gross lesions observed in experimentally infected horses are hemorrhages—usually petechiae and ecchymosis—and edema. Edema is found in the legs, ventral abdominal wall, and prepuce. Hemorrhages are most common in the subcutaneous tissues, fascia, and epimysium of the distal limbs. Histologically, the small arteries and veins are inflamed, primarily those in the subcutis, fascia, and nerves of the legs and in the ovaries, testes, and pampiniform plexus. Vascular lesions may be proliferative and necrotizing, with swelling of the endothelial and smooth muscle cells, cellular thromboses, and perivascular accumulations primarily of monocytes and lymphocytes and, to a lesser extent, of neutrophils and eosinophils. Mild inflammatory vascular or interstitial lesions have also been reported in the kidneys, heart, brain, and lungs of animals necropsied during the course of the disease. The ventricular tachycardia and premature ventricular contractions occasionally observed in affected horses are thought to be associated with myocardial vasculitis. Fur-

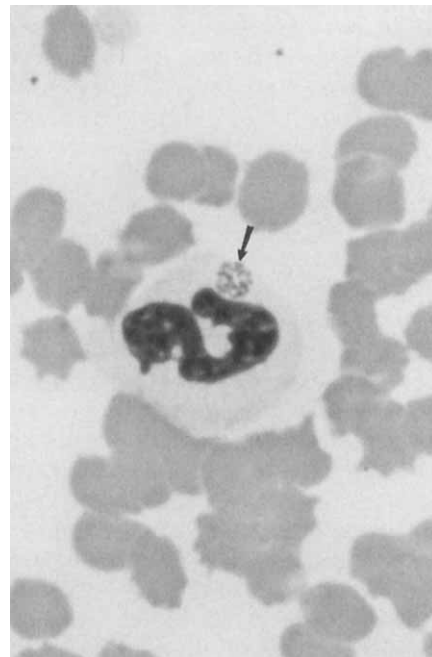
thermore, horses with chronic bacterial infections may develop an exacerbation (e.g., bronchopneumonia, arthritis, pericarditis, lymphadenitis, cellulitis) of the preexisting lesion.

## **IMMUNITY**

Immunologic studies with *A. phagocytophila* indicate both a cell-mediated and a humoral immune response to clinical infection. Horses that recover from experimental infections develop humoral and cell-mediated immune responses by 21 days after infection. In naturally infected horses, antibody titers peak 19 to 81 days after the onset of clinical signs. Immunity persists for at least 2 years and does not appear to depend on a latent infection or carrier status. Blood from previously infected and naturally recovered or tetracycline-treated horses is not infectious.

## **DIAGNOSIS**

Diagnosis is based on awareness of geographic area for infection, typical clinical signs, abnormal laboratory findings, and characteristic morulae in the cytoplasm of neutrophils and eosinophils in a peripheral blood smear stained with Giemsa or Wright's stain (Figure 2.13-1). Because horses are leukopenic, a greater percentage of neutrophils can be examined by use of the buffy coat preparation and subsequent staining. The number of cells that contain morulae varies from less than 1% of cells initially to 20% to 50% of the neutrophils by days 3 to 5 of infection. Alternatively, an indirect fluorescent antibody test is available, and paired titer testing with a significant (four-fold or greater) rise in antibody titer to *A. phagocytophila*



**Figure 2.13-1** *Anaplasma phagocytophila* inclusions (arrow) in a neutrophil of a horse with equine granulocytic ehrlichiosis (EGE; buffy coat smear, Giemsa stain, magnification  $\times 1000$ ).

can be performed to retrospectively confirm recent exposure. However, because inclusion bodies are always visible during the midstage of the febrile period, antibody testing is not required to make a definitive diagnosis of horses in endemic areas or after recent visits to endemic areas. Recently, several polymerase chain reaction (PCR) assays have been developed for members of the *A. phagocytophila* genogroup and found to be highly sensitive and specific. The detection through PCR analysis is useful for the diagnosis of EGE, particularly during early and late stages, when the number of organisms is too small for diagnosis by microscopy.

## TREATMENT AND PREVENTION

The intravenous (IV) administration of oxytetracycline at a rate of 7 mg/kg body weight once daily for 5 to 7 days has been an effective treatment for EGE. Prompt improvement in appearance and appetite and a drop in fever can be noted within 12 hours of treatment. Indeed, a failure of defervescence within 24 hours would strongly point to another cause for illness. On rare occasions, horses treated for fewer than 7 days relapse within the following 30 days. When untreated, the disease can be self-limiting in 2 to 3 weeks when no concurrent infection is present, but weight loss, edema, and ataxia are of increased severity and are

prolonged. In treated horses, ataxia persists for 2 to 3 days, and limb edema may persist for several days. Inclusion bodies generally are difficult to find after the first day of treatment and are no longer present within 48 to 72 hours. Supportive measures are recommended in severe cases, including fluid and electrolyte therapy, supportive limb wrap, and stall confinement of severely ataxic horses to prevent secondary injury.

The prognosis in EGE is considered excellent in uncomplicated cases—in sharp contrast to the other diseases on the list of differential diagnostic considerations. At present, no vaccine against EGE is available; thus prevention is limited to observance of tick-control measures.

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## SECTION III

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### Gastrointestinal Diseases

*Edited by Dr. Anthony T. Blikslager*

#### CHAPTER 3.1

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### Correction of Common Dental Malocclusions with Power Instruments

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Proper dental care is essential to maintain a healthy horse, and regular dental prophylaxis should be included in every horse's preventive healthcare program. For years, many veterinarians ignored common equine dental malocclusions because of lack of education, observation, and proper instrumentation. Malocclusions, or the improper position and contact between teeth, lead to inefficient chewing, decreased performance, and premature loss of teeth. Many horses do not show signs of dental problems until it is too late to correct them. If not corrected, all malocclusions will progressively become more severe. Regular dental care can prevent malocclusions from forming, and correction of overgrowths can allow recovery of excessively worn teeth.

With the advent of modern power instrumentation, equine dentistry has become much more accurate and potentially less traumatic to the horse. However, because power instruments can rapidly cause an extreme amount of damage to the horse's dentition with little effort on the clinician's part, the clinician must obtain proper instruction before undertaking their use to correct a dental problem. Power instruments do not necessarily speed up the procedure as much as they allow precise, atraumatic removal of overgrowths. The objective should be to remove only the areas of overgrowth while maintaining as much of the normal areas of occlusion for future wear. In this author's opinion "less is more" with the use of power instruments in equine dentistry. It is much better to do a little work on the entire mouth and return later to do more, than it is to do a large amount in limited areas and have an uncomfortable horse. Modern instruments allow the user to remove tooth enamel in millimeter increments on just a portion of one tooth instead of inappropriately re-

moving a generalized area of many teeth. For example, a single high transverse ridge can be removed from the occlusal surface of one tooth while the normal transverse ridges are maintained on adjacent teeth.

Another objective of treatment should be to traumatize as little soft tissue as possible. Soft tissue trauma in the mouth causes swelling, pain, and dysphagia—resulting in a very uncomfortable horse and an unhappy owner. When power instruments are being used, it is important to steady the instrument with a pivot or anchor point by resting the instrument on the speculum or soft tissues. This procedure permits improved accuracy and prevents fatigue. Being able to see the entire procedure is very important when power instruments are involved. If used correctly, modern instruments cause minimal trauma.

#### SELECTION OF INSTRUMENTATION

A multitude of different power instruments are available, and new designs are constantly being made. Power instruments can be divided into reciprocating-type blades, rotary-type disks, and burrs. Thermal trauma to teeth due to heat created from power instruments is a definite concern. Sharp burrs cut teeth very quickly without creating detrimental heat. The use of a burr, disk, or blade that does not load up with tooth material is desirable. If an instrument becomes loaded with tooth material, it does not cut as well as it should and creates more heat than is necessary.

Power instruments are similar to hand floats in that one or two instruments cannot access all areas of the mouth. When purchasing instruments, the practitioner should consider a combination of the different designs. The idea should be to find the combination with which

the user is most comfortable and that is designed to create the least amount of trauma while permitting the greatest degree of accuracy in all areas of the mouth.

## DENTAL EXAMINATION

Clinicians should develop a routine used to examine the mouth and perform dental procedures. Following a routine results in greater efficiency and lowers the likelihood of problems being overlooked. The entire head should be examined for symmetry and the presence of painful areas. A cursory examination can be performed on an unsedated horse, but chemical restraint is advised for a complete examination. A thorough examination must include the use of a full-mouth speculum. This examination should include a visual examination using a bright light source. A retractor can be used to examine all the soft tissues and dentition. Gums, cheeks, tongue, and palate should be checked for ulcers, foreign objects, scar tissue, tumors, and periodontal disease. The teeth should be observed for fractures, decay, excessive wear from opposing overgrowths, and diastema or spaces between the teeth. Digital palpation should include checking each tooth for looseness and palpation of the soft tissues for ulcers, scars, and periodontal disease. Palpation also should include the interdental space to check for wolf teeth (see Figure 3.1-4, *B*), blind or impacted wolf teeth, or bit damage to the underlying bone. A foul odor may indicate pocketing of feed, retained deciduous teeth, periodontal disease, or the presence of infection.

Examination should include lateral manipulation of the mandible while the upper and lower jaws are forced together. The quality of grind can be evaluated as the examiner listens to the contact, and lack of lateral excursion can be determined as overgrowths inhibit lateral freedom. Lateral excursion and the quality of occlusion can also be detected by use of a cheek retractor and observation of the occlusal surface of the upper molars while the lower jaw is moved to each side. This allows the examiner to observe dominant areas of occlusion that may not be readily seen with the mouth open. A horse masticates by dropping the mandible, moving it laterally, and closing the mouth to bring the upper and lower occlusal surfaces together.

## CHEEK TEETH MALOCCLUSIONS

### Sharp Enamel Points

Sharp enamel points develop on the buccal side of the upper cheek teeth and the lingual side of the lower teeth because of lack of lateral excursion. These upper and lower enamel points can easily be removed, along with a small portion of the cingula or ridges on the buccal side of the upper teeth. Removal of these points decreases trauma to the soft tissues and permits increased lateral excursion. Care must be taken to maintain as much of the normal occlusal surface as possible. Rounding or doming the occlusal surface is incorrect and decreases the amount of occlusal surface area available to grind feed.

Many instruments do not provide easy access to the buccal aspect of the cheek teeth. Because of the intimate contact with the soft tissues, the most common cheek ulcerations occur from sharp enamel points and cingula of

the caudal two molars (110, 111, 210, 211 Triadan system; Figure 3.1-1). Proper instrumentation must be used to access this area. Many full-mouth specula push in on the cheeks, further limiting access to this caudal region of the mouth. The speculum can be partially closed to relax the cheeks and allow more room for access. Small, low-profile reciprocating blades at the proper angle permit the easiest access to the buccal aspect of the caudal molars. The motor running the blade should have a stroke less than 12.5 mm to decrease the chance of soft tissue trauma. Trauma to the soft tissue beyond the last molar can lead to severe infection and abscessation.

Another frequently encountered area of soft tissue trauma is the premolar region in the rostral portion of the mouth. Most of this trauma is associated with bridles, nosebands, and bits. In most horses the second premolar is positioned at an angle toward the palate in relation to the adjoining teeth. Care must be taken to sufficiently round and smooth these teeth to provide adequate comfort. The cingula can be completely smoothed to the gum aspect along the buccal portion of the second and third premolars (106, 107, 206, 207). The rostral third of the upper and lower premolars can be rounded back in a smooth, convex radius to provide comfort in horses wearing a bit ("bit seat").

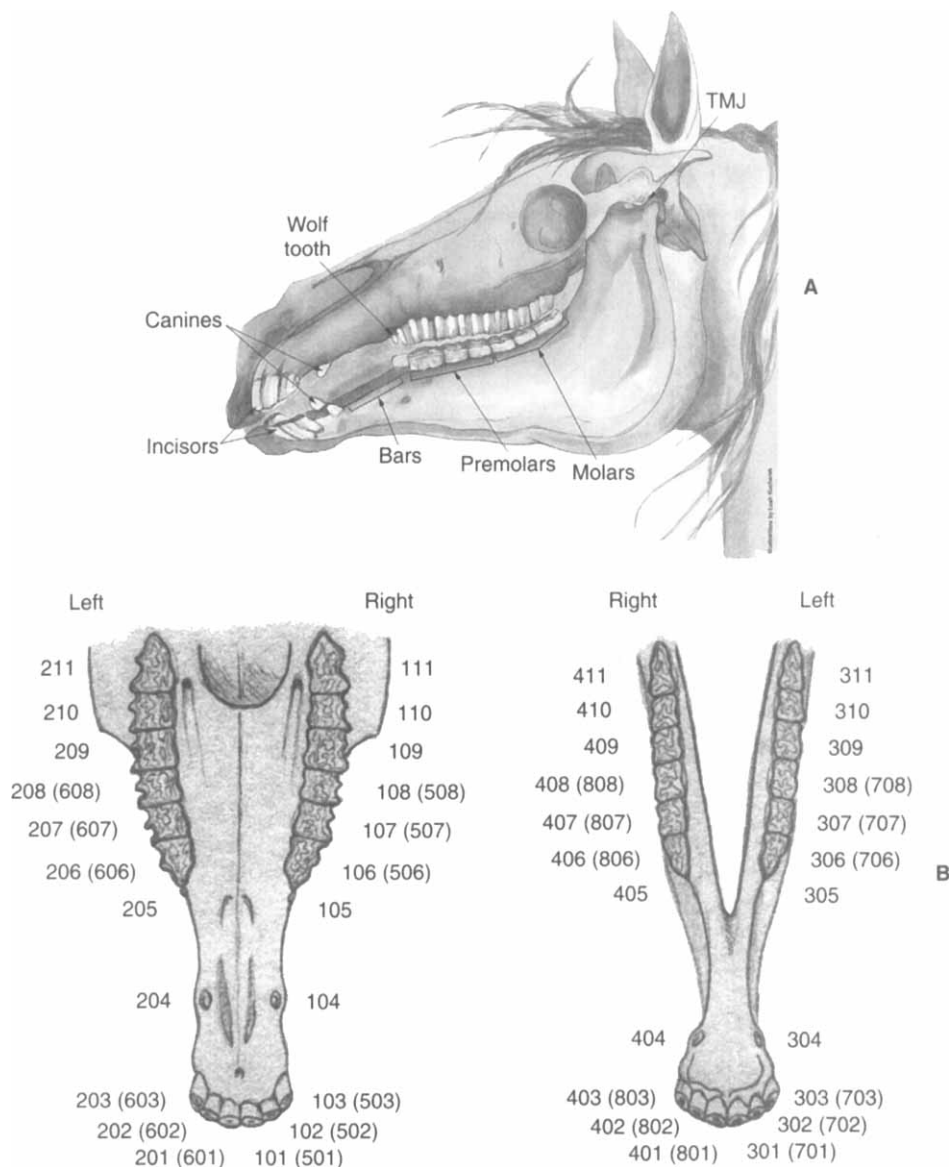
### Molar Table Angle

The occlusal surfaces of the cheek teeth are normally angulated away from the horizontal axis because the maxillary teeth rows normally are 30% further apart than their mandibular counterparts. In addition, the maxillary cheek teeth are wider than the mandibular teeth and have approximately 30% more occlusal surface. The degree of normal angulation varies, depending on the conformation of the individual horse. As a horse chews with less lateral excursion than normal, the molar table angle becomes steeper (Figure 3.1-2). As mentioned previously, simply removing overgrowths such as sharp enamel points permits a horse to chew with more lateral excursion. In the case of more severe overgrowths or malocclusions, more aggressive occlusal surface reduction is required.

Maintaining the normal occlusal table angle across the entire occlusal surface, from lingual/palatal to buccal, is extremely important when these malocclusions are addressed. The clinician should choose a portion of the occlusal surface that appears normal and match the overgrown areas to the normal angulations as closely as possible. In severe cases of steep angulations or sheared molar tables, this process may take several visits over the span of 1 year. Maintaining as much of the normal occlusal surface as possible is important. A cheek retractor should be used with the mouth in a closed position to check for proper occlusion and for accuracy between the two occlusal planes.

If a horse is primarily chewing on one side of its mouth, the contralateral molar table angle will become sheared and the side with more lateral excursion will remain flatter. Horses can begin to avoid chewing on one side of the mouth for one of the following reasons:

1. Pain and trauma occurring from sharp enamel points
2. Prevention of free lateral excursion due to either another malocclusion or an injury to dentition or to the temporomandibular joint

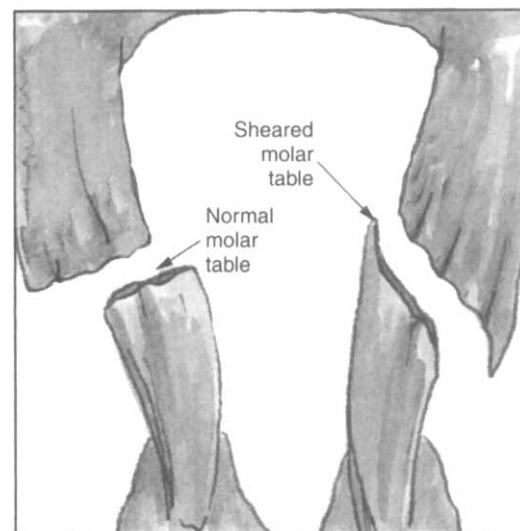


**Figure 3.1-1** A, Nomenclature of horse teeth. B, Triadan system of dental nomenclature. Deciduous teeth are listed in parentheses. The upper jaw is shown on the left, with the lower jaw on the right.

In most cases, correction of the malocclusion and the molar table angle permits the horse to chew with increased lateral excursion. These horses should be examined regularly to maintain proper excursion and occlusion.

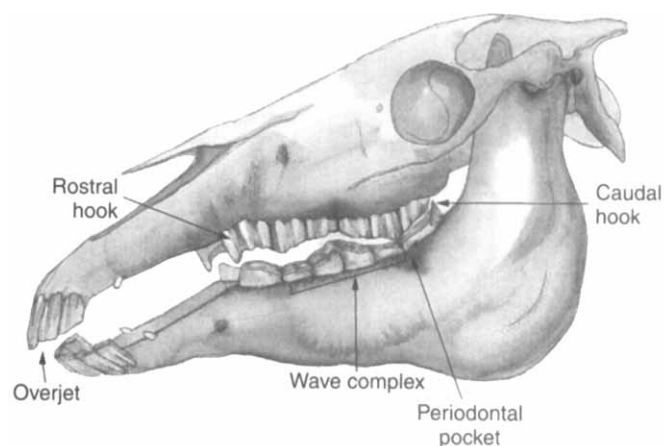
### Hooks

Observing and palpating each arcade is important. Hooks on the upper second premolars (106, 206) can interfere with biting, and both rostral upper and caudal lower hooks (311, 411) cause the mandible to move caudally, creating stress on the temporomandibular joint (Figure 3.1-3). These hooks also can limit rostral to caudal slide of the molar arcades over each other as the horse raises and lowers its head, a motion that can prove extremely important in a performance horse as it is asked to change head position or to go in a "frame." These types of malocclusions can limit a horse's ability to freely change head position, or at the very least, make such changes quite uncomfortable.

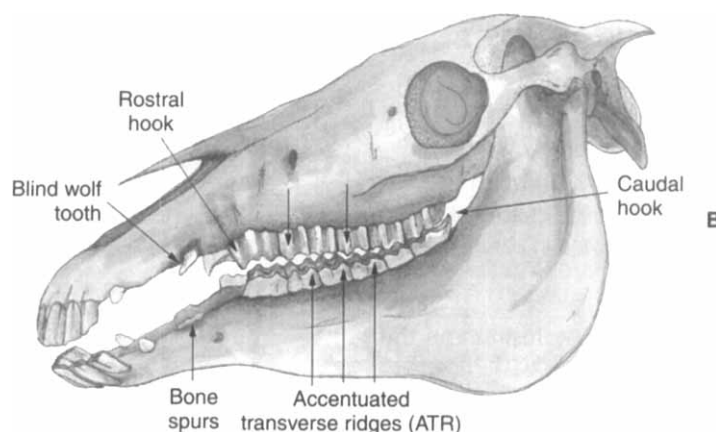
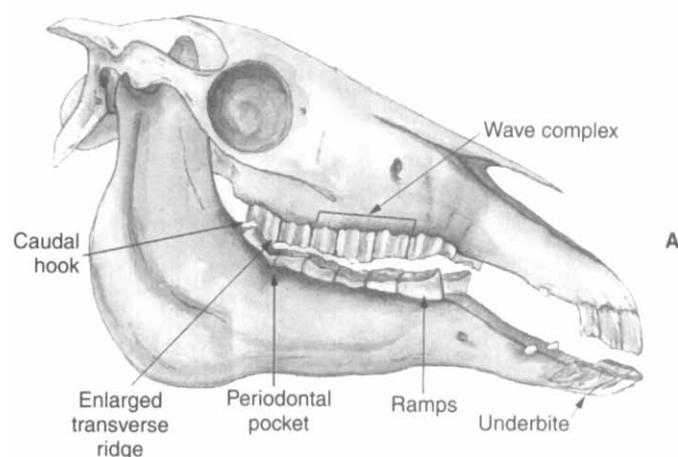


**Figure 3.1-2** Molar table angle showing the sheared molar table on the right.

**Figure 3.1-3** Rostral and caudal hooks with a typical wave complex.



**Figure 3.1-4 A**, Rostral ramps with caudal upper hooks, enlarged transverse ridge, and wave complex. **B**, Blind wolf tooth, bone spurs, caudal and rostral hooks, and accentuated transverse ridges.



Rostral hooks are best observed from the palatal aspect and should be reduced to the normal occlusal plane of the adjoining teeth. Many lower third molar (311, 411) infections have resulted from improper use of molar cutters or inadvertent fractures caused by these instruments. Many such teeth were not actually hooked, but the curvature of the jaw made it appear as though the caudal aspect of the tooth were high (Curve of Spee), and the molar cutter caused an inadvertent fracture into the pulp chamber of the tooth. Molar cutters have become obsolete with the advent of advanced power instruments, the latter of which permit the clinician to accurately remove only as much

tooth as necessary without entering the pulp chamber of the tooth. In the case of large hooks the entire overgrowth does not have to be removed at one time, as long as after reduction there is no interference with lateral excursion. If the pulp chamber is entered, the tooth often dies over time. An open pulp chamber should be packed with calcium hydroxide powder and finished with a tooth sealant.

### Ramps

Ramps most often occur on the lower second premolars (306, 406) and may occur when deciduous upper second



premolar caps (106, 206) are retained; they may also be secondary to excessive reduction of the upper second premolars. Ramps can cause severe discomfort from the bit as the tongue and cheeks are pulled into these dominant teeth. Ramps can also force the mandible forward over time, creating an underbite and extreme pressure on the temporomandibular joint (Figure 3.1-4). Premolar ramps (306, 406) should be reduced to the level of the occlusal plane of the adjoining normal teeth, and the rostral aspect should be rounded properly to provide comfort with the bit.

The clinician must take care to reduce the proper amount of tooth from the second rostral premolars and the last caudal molars. If the second premolars (106, 206, 306, 406) or last lower molars (311, 411) are reduced to the gum level, the rostral or caudal edges of the teeth will become extremely sharp as the reserve crown continues to erupt above the gum. Overreduction of one tooth can create a malocclusion by allowing the opposing tooth to become dominant. Overreduction on an older horse may prevent the teeth from ever attaining occlusion again. If uncertain of how much tooth to reduce, the clinician should perform the reductions in the following stages:

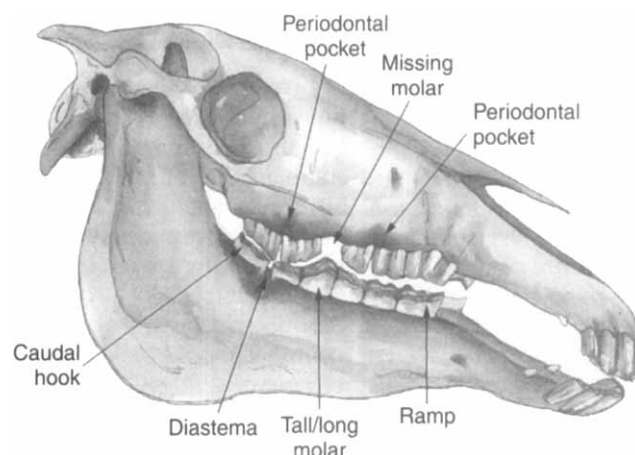
1. Reduce a small amount of tooth.
2. Remove the speculum and observe occlusion with the aid of a cheek retractor as the cheek teeth are moved into occlusion.
3. If the tooth still appears to prevent proper lateral excursion, repeat the procedure.

### Canine Teeth

Tall and/or sharp canine teeth should be rounded and filed smooth, and any calculus should be removed. Sharp canines can be blunted before the back of the mouth is palpated to reduce risk of laceration to the examiner's arm or wrist. Other benefits of blunting canines include less chance of injury by catching on fixed objects, less injury during fights, and easier insertion and removal of the bit. Power burrs work well to reduce and round canines. The clinician should not reduce canines to gum level because in most cases this procedure can lead to entry into the pulp chamber and death of the tooth over a period of many years. In addition, canine teeth that are reduced to gum level tend to collect more calculus, causing irritation to the gums and decay to the tooth. A horse may stick its tongue out of the corner of its mouth after the canines are reduced to the gum level, causing the horse to be marked down in the show ring. Canines should be reduced to approximately half their normal mature height so that approximately 1 cm is left exposed.

### Tall or Long Teeth

Usually tall or long teeth develop from lack of occlusion, which is often caused by loss of the opposing teeth (Figure 3.1-5). The best way to reduce these teeth is with power instruments that feature a sharp, solid carbide burr. Care must be taken not to overheat the tooth if a large amount must be reduced. The clinician can spray the tooth with



**Figure 3.1-5** Tall or long molar and diastema created by missing molar.

water or reduce part of the tooth and move on to another area in the mouth, returning to the tooth after several minutes. Tall or stepped teeth often cause the horse to use only one side of its mouth, leading to excessive wear on one arcade and a sheared molar table on the other. The incisors may also be offset or at a diagonal. The owner must be made aware that these malocclusions need to be corrected regularly.

### Wave Complexes

Wave complexes involve many premolars and/or molars, creating a wavelike appearance in the row of teeth (see Figures 3.1-3 and 3.1-4), often occurring secondary to other malocclusions such as those caused by retained deciduous caps, missing teeth, hooks, and ramps. Wave complexes also result from the horse not being able to chew freely side to side; they progressively worsen. The upper rows of teeth have a curvature in the palatobuccal plane from rostral to caudal, whereas the lower rows of teeth are relatively straight (see Figure 3.1-1). With decreased lateral excursion the lower fourth premolar and first molar (308, 309, 408, 409) become high on the lingual side because they lack occlusion on the palatal aspect of the curvature. The first upper molars (109, 209) can further contribute to the formation of a wave complex in the aged horse. These are the oldest teeth in the horse's mouth and generally are the first to wear beyond their enamel, allowing the opposing lower molars (309, 409) to become dominant.

Correcting these waves early in horses less than 10 years of age and preventing the excessive wear that wave complexes cause to many teeth are the best ways to solve this problem. The clinician can use power instruments to reduce these high complexes while maintaining a proper molar table angle. Care must be taken to encourage lateral excursion and also maintain adequate occlusion. Because a number of teeth are involved, frequently these waves require correction in stages. In many older horses the wave complexes will never be completely corrected, but over many years with good dental maintenance they will gradually improve.

## Transverse Ridges

Transverse ridges across the occlusal surface of the cheek teeth are a natural occurrence on horses' teeth. Normal transverse ridges increase the surface area available for grinding. The normal occlusal surface is composed of an intricate pattern of hard enamel folds between softer dentin and cementum. A shift in jaw alignment may result in the development of enlarged ridges because areas with more enamel erode areas containing less enamel in the opposing tooth. These overly enlarged ridges can interfere with normal chewing motion and rostral to caudal movement of the jaw. The examiner should look for uniformity in the height of the transverse ridges and try to leave the normal ridges alone and reduce only the high ones. Reducing the transverse ridges completely can lead to too much rostral to caudal slide as the horse masticates. This increased rostral to caudal movement may create diastema between the second and third premolars (306/307, 406/407) and/or between the second and third molars (310/311, 410/411). An enlarged transverse ridge can mechanically force two opposing teeth apart and create a diastema. A common place for this to occur involves the second upper molar (110, 210); an enlarged transverse ridge forces a space between the lower second and third molars (310/311, 410/411; see Figure 3.1-4).

## INCISORS

Many incisor abnormalities cause difficult mastication, decrease performance, or both. The incisors are easily examined and corrected due to their easy accessibility. Most abnormalities can be corrected or greatly improved with relatively simple procedures and equipment. Abnormalities of the incisors include retained deciduous teeth; tall or long teeth; or misaligned, deformed, and unerupted teeth.

Deciduous incisors that are retained should be extracted if (1) the opposing incisor is permanent and in wear, (2) the contralateral incisor is permanent and in wear, or (3) the permanent incisor is erupting behind the deciduous incisor. The retained incisors should be extracted, along with any root fragments, to permit the permanent incisor to move into its proper position for improved occlusion. The adjoining teeth often may need their corners trimmed with a diamond wheel, small burr, or hand file to allow the permanent tooth room to migrate into its proper position.

Individual incisors usually become long or tall when the opposing tooth is missing. A long or tall incisor should be shortened so that its occlusal surface is level with that of the other incisors. Tall or long incisors interfere with the lateral movement of the mandible during mastication and may cause less premolar and molar occlusion. Power instruments have greatly improved the accuracy and ease with which multiple incisors are leveled.

The occlusal plane should be level from side to side. A variety of conditions can result in uneven incisor occlusal planes. If not too severe, the bite abnormalities can be corrected immediately. However, if the misalignment is severe, several procedures over an extended period of time may be necessary to totally level the incisors. The incisors should not be shortened so much that a gap remains be-

tween the upper and lower central incisor occlusal planes, causing full cheek teeth occlusion. The cheek teeth should not be in occlusion when the incisors are in a centric, closed position. Again, care should be taken to not enter the pulp chamber when incisors are reduced.

Many people believe that horses' incisors become long from lack of grazing. Although the incisors may lengthen in many stalled horses, the molars do so as well—possibly a result of or an adaptation to domestication. Research has shown that the more coarse and dry the feed material, the less a horse chews with full lateral excursion. By so doing, the molar table angle tends to become steeper and the molars and incisors become longer. Added molar length may benefit the horse by keeping coarse, dry feed material from abrading the gums. Conversely, taller molars with increased table angle can, to the detriment of the horse, prevent proper grinding of feed, proper lateral excursion, and normal wear of the teeth. The goal should be to accurately remove only the overgrowth on the premolars and molars and reduce the incisors just enough to level them if possible, and provide adequate molar occlusion.

Brachygnathia (Figure 3.1-6) or parrot-mouthed horses (horses that do not have occlusal contact of the upper and lower central incisors) may need their mandibular incisors shortened to reduce trauma to the palate. More importantly, the incisors have to be reduced to prevent the "locking effect" that occurs when the mandibular incisors become trapped inside the maxillary incisors. Some parrot-mouthed horses have no lateral excursion and only are able to chew up and down, which leaves only a small portion of the molar table in contact and leads to poor mastication. Often the upper and lower incisors that have no occlusion must be reduced almost to the gum level. Parrot-mouthed horses may have more problems with mastication because of the long hooks that will most likely develop on the second upper premolars (106, 206) and the third lower molars (311, 411) as a result of the overbite—proving the importance of a complete dental examination and all indicated corrective procedures.

Foals born with or developing an overbite may benefit from help at an early age. Hooks should be removed and incisors shortened to permit free lateral excursion. The foal should be fed hay and grain on the ground to encourage rostral movement of the mandible. Severe parrot-mouth can be improved at an early age (4-6 months) with a technique developed by Dr. Jack Easley involving installation of an acrylic bite plate and retaining wires.

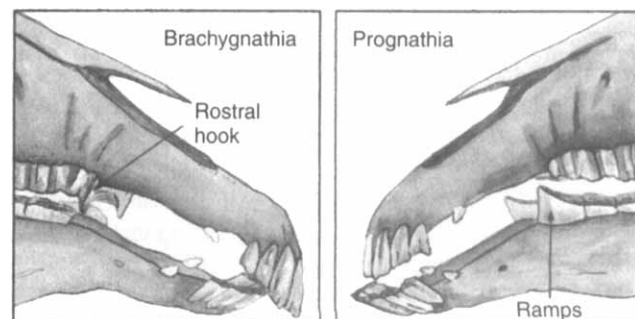


Figure 3.1-6 Brachygnathia (left) and prognathia (right).

Prognathia (see Figure 3.1-6) or underbites should be addressed in a similar manner. Ramps may need to be reduced on the second lower premolars (306, 406) and the last upper cheek tooth (111, 211). Foals may benefit from feeding in an elevated position to encourage the lower jaw to move caudally.

Ventral curvatures can be addressed by the removal of more tooth off the lower corner than the remaining incisors. Dorsal curvatures require removal of the overgrown portion of the upper corner incisors. Diagonal or offset incisors require the clinician to address one side of the upper incisors and the opposite side of the lower incisors (Figure 3.1-7).

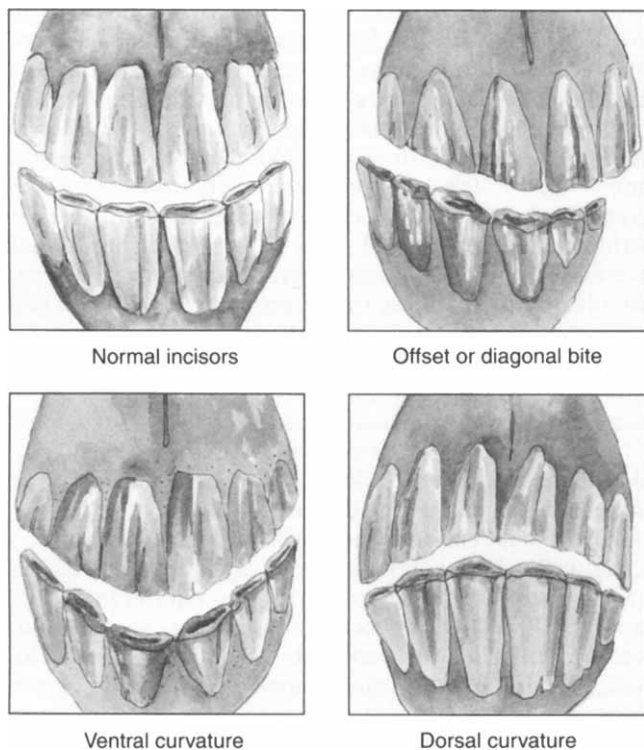
As stated previously, removal of *only* the amount of tooth necessary to gain free lateral excursion and proper molar occlusion is important. Removal of too much incisor may damage molars because of excessive occlusion. Increased pressure on individual molars can cause them to shift or fracture or diastema to form. Too much occlusion may cause pain and dysphagia.

If enough incisor is not removed, the horse may not have adequate molar occlusion to grind feed properly. After the molar malocclusion is addressed, if the incisors do not separate within 1 cm of lateral movement, too much occlusion may be present on the incisors; in this case the horse is forced to chew with an increased amount of lateral excursion to obtain molar occlusion. Excessive lateral excursion results in the molars becoming short and the

molar table angle becoming extremely flat. An excessive amount of lateral excursion can cause some cheek teeth to shift laterally. The increased occlusion on the incisors causes them to rapidly reduce in height. The increased lateral pressure on the incisors during mastication can cause diastema to form between them. Over a period of time the horse will demonstrate short incisors and short molars due to the abnormal forces.

In this author's opinion, the incisors should separate after moving the mandible laterally 5 to 10 mm. In geriatric horses with multiple expired teeth, lateral slide greater than 10 mm may be acceptable. Accurate molar adjustment makes the removal of much of the incisors unnecessary.

Guidelines for the amount of tooth that should be removed or should remain are difficult to determine and must be applied individually. Cingula and transverse ridges are normal occurrences on teeth, as are sharp enamel edges, and both structures enable a horse to properly grind course forages. Teeth that are made perfectly smooth cannot grind feed properly. Each horse has its own individual conformation and its own set of malocclusions. The main objective should be to diagnose malocclusions early, correct the malocclusions as soon as possible, and maintain the corrections over the life of the horse. The earlier a correction can be performed, the less tooth needs to be removed, allowing the horse to better maintain its own teeth by masticating properly. In a horse with severe malocclusions, attempts to correct all problems at once can be detrimental to the animal's health. Many severe malocclusions should be corrected slowly over many years.



**Figure 3.1-7** Incisor malocclusions.

### Supplemental Readings

- Baker GJ, Easley KJ (eds): *Equine Dentistry*, Philadelphia, WB Saunders, 1999.
- Dixon PM, Tremaine WH, Pickles K et al: Equine dental disease Part I: a long-term study of 400 cases: disorders of incisors, canine and first premolar teeth. *Equine Vet J* 1999; 31:369-377.
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## CHAPTER 3.2

# Differential Diagnosis of Oral Ulceration

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Oral ulceration is seen infrequently in horses, and diagnosis of the cause can be difficult. The ulceration can develop from vesicles, which may erode and become painful. A thorough history must be taken to assess recent exposure history, including treatments and foodstuffs. In addition, physical examination and serology can narrow the list of differential diagnoses, which is extensive.

### VESICULAR STOMATITIS

Vesicular stomatitis (VS; see Chapter 2.6: "Vesicular Stomatitis") is a viral disease that can affect horses, other equids, cattle, pigs, llamas, and humans. In the United States the disease primarily affects horses and cattle. Two serologically distinct VS viruses exist: (1) VS virus serotype Indiana (VSV-Indiana) and (2) VS virus serotype New Jersey (VSV-New Jersey). The disease occurs sporadically in the United States, except in Ossabaw Island, Ga., where it is endemic. In the United States, VS outbreaks tend to occur between early summer and fall. Transmission of the virus is by direct contact with lesions or saliva of infected animals or contaminated fomites, especially if the contact is with abrasions on the susceptible animal, particularly on the teats or coronary bands. Insects also may act as potential vectors. The incubation period for VS is 3 to 15 days (1 to 3 days after experimental inoculation), after which lesions appear as blanched areas, which then develop into vesicular lesions up to 2 cm in diameter, become ulcerative, and sometimes erode. They can occur on the nasal or oral mucosa, dorsal surface of the tongue, mammary glands, external genitalia, or coronary bands. The first clinical signs noted by owners of infected animals are typically anorexia and excessive salivation. Other signs include swollen lips and muzzle, crusting lesions, and lameness. Fever is seen with the initial infection. However, by the time lesions appear, fever is not usually present. Secondary bacterial infection of these lesions may occur.

The virus is usually shed for 6 to 7 days from active lesions. Uncomplicated lesions usually resolve in 7 to 14 days. Younger animals (<1 year of age) appear to be less susceptible. The morbidity rate is usually 5% to 10% but can reach 80% in dairy cattle. In uncomplicated cases, mortality is generally zero. VS can be diagnosed only by detection of the virus from active lesions or serology. The best specimen for virus isolation is epithelium from unruptured or freshly ruptured vesicles. Numerous serologic

tests are available, including serum neutralization (SN), complement fixation (CF), and a competitive enzyme-linked immunosorbent assay (cELISA). Histopathologic findings, including hyperplastic epidermis, intercellular and intracellular epidermal edema, reticular degeneration, spongiotic microvesicles, and focal necrosis are nonspecific and usually do not aid in diagnosis.

### OTHER VIRAL CAUSES OF ORAL ULCERATION

Oral ulceration occurred in an outbreak of equine viral arteritis (EVA) at a riding establishment in Spain in 1992. Infection occurs via aerosolization into the respiratory tract or venereally. The incubation period is 3 to 14 days or 6 to 8 days if transmitted venereally. Horses are usually febrile for 1 to 5 days, and clinical signs include anemia, depression, cough, limb edema (especially of the hind limbs), nasal and ocular discharges, conjunctivitis, rhinitis, and periorbital or supraorbital edema. Edema of the scrotum and prepuce can occur in the stallion and abortion in the mare (up to 50% in exposed mares between 3 and 10 months of gestation). Death may occur in foals. The only other consistent clinical signs in the Spanish outbreak were mild ventral and limb edema. Laboratory diagnosis involves virus isolation and/or serologic tests. Acute EVA can be diagnosed by virus isolation from nasopharyngeal swabs or washings from the buffy coat of ethylenediaminetetraacetic acid (EDTA)-treated or citrated blood samples. Virus isolation often can be unsuccessful. CF and virus neutralization tests also can be used. Demonstration of seroconversion to EVA in acute and convalescent-phase sera helps to confirm the diagnosis (see Chapter 2.6).

Other viral causes associated with oral ulceration include calicivirus, equine adenovirus, equine herpesvirus (EHV), Jamestown Canyon virus, and equine infectious anemia. EHV-3 causes coital exanthema, a contagious venereal disease. It is transmitted via coitus, fomites, inhalation, and insects. Papules appear on the vulva or perineum of mares and the penis and prepuce of stallions. The papules then can progress to vesicles, bullae, or pustules. Vesicles or bullae also can be found in the oral cavity, in the nostrils, or on the lips. Diagnosis is based on clinical signs, virus isolation, and skin biopsy. Histologic evidence includes hyperplastic superficial and deep perivascular dermatitis with ballooning degeneration and eosinophilic intranuclear inclusion bodies.

Jamestown Canyon virus was found in one horse during an outbreak of VS in Colorado in 1997. The clinical signs were indistinguishable from VS in this case. Diagnosis was achieved via electron microscopy. Equine infectious anemia can cause a necrotizing vasculitis, which can result in oral ulceration. Clinical signs include fever, icterus, petechial hemorrhages, ventral edema, anemia, and weight loss. Diagnosis is confirmed by a Coggins test (agar gel immunodiffusion).

## CONDITIONS OF THE SKIN

Bullous pemphigoid is an autoimmune skin disease of the horse characterized by vesicles and pustules on the epithelium of the head and neck, including the oral mucosa, usually at the mucocutaneous junction. Lesions also can occur in the axilla or groin or on the limbs. Fever, anorexia, pruritus, and pain may be seen. The disease is caused by the development of autoantibody against a component of the basement membrane of the epithelium. A diagnosis is based on history, physical examination, and skin biopsy. The biopsy has to be from intact bullae to be beneficial. Histologic evidence includes subepidermal vacuolar alterations and subepidermal clefts and vesicles. Neutrophilic and eosinophilic infiltration of the superficial epidermis also may occur.

Exfoliative eosinophilic dermatitis and stomatitis is an idiopathic disease characterized by ulcerative stomatitis, severe wasting (not seen in bullous pemphigoid), marked exfoliation, and eosinophilic infiltration of the skin. Diagnosis is made on the basis of history, physical examination, and skin biopsy. Skin biopsy reveals superficial and deep eosinophilic and lymphoplasmacytic dermatitis with marked irregular epidermal hyperplasia. A chemistry panel can show hypoproteinemia, hypoalbuminemia, and elevated  $\gamma$ -glutamyl transferase and serum alkaline phosphatase concentrations.

A mucocutaneous form of paraneoplastic syndrome producing signs of bullous stomatitis has been reported. The oral lesions were characterized histologically as subepidermal clefting. Their development coincided with that of a hemangiosarcoma on the right side of the mid-cervical region. The lesions resolved after the mass was removed.

Erythema multiforme produces cutaneous lesion patterns that are usually bilaterally symmetric. Lesions in the horse can be urticarial and occasionally vesiculobullous and ulcerative. They usually are found on the trunk and distal extremities and rarely around the oral cavity. Some of the lesions resemble wheals, but unlike the wheals of urticaria, they persist for days to weeks. A lot of cases are idiopathic, but some have been associated with drug administration, such as trimethoprim-sulfonamides; pregnancy; neoplasia; connective tissue disease; and infections. Diagnosis is based on history, clinical signs, and skin biopsy. Histopathologic findings include hydropic interface dermatitis with necrosis of individual keratinocytes. Coagulation necrosis also is seen in the vesiculobullous form.

In rare instances vasculitis may cause signs of oral ulceration. Areas of cutaneous edema, which then can progress to ulcerative or erosive lesions, characterize vas-

culitis. Causes of vasculitis include purpura hemorrhagica (usually after equine influenza virus [EIV] or *Streptococcus equi* subsp. *equi* infection), EVA, equine infectious anemia, and equine ehrlichiosis. Common signs of purpura hemorrhagica include edema of the limbs, ventral abdomen, head, and trunk. Petechial hemorrhages also may be seen. A skin biopsy that shows leukocytoclastic venulitis in the dermis and subcutaneous tissues helps support the diagnosis. The history may reveal recent exposure to *S. equi* subsp. *equi* or EIV infection. Measurement of an antibody titer to *S. equi* subsp. *equi* or demonstration of seroconversion to EIV in acute and convalescent-phase sera helps confirm the diagnosis.

*Anaplasma phagocytophila*, a rickettsial organism, may be associated with oral ulceration. Other, more common clinical signs include anorexia, fever, depression, petechial hemorrhages, edema of the limbs, thrombocytopenia, and anemia. Diagnosis is confirmed by the finding of pleomorphic inclusion bodies in the cytoplasm of circulating neutrophils and eosinophils.

## OTHER CAUSES OF ULCERATION

Allergic reactions to drugs and toxic chemicals can cause oral ulceration. Exposure to bedding containing wood chips from the Simaroubaceae family, such as bitterwood and quassia, has been associated with oral ulceration. Additionally, dry, cracked areas around the nose, lips, and anus may be observed. Systemic signs also have been seen, including anorexia, jaundice, and hematuria. A thorough history, including any recent changes in bedding, aids in the diagnosis.

Physical trauma causing oral ulceration after the ingestion of plant awns, coarse forages, and triticale hay has been reported. Plant awns may be found in the ulcerated areas on physical examination. *Setaria lutescens* (yellow bristle grass or foxtail) also has been associated with outbreaks of oral ulceration in California and New York. A thorough history and examination of feedstuffs, especially the hay, helps with the diagnosis.

Cantharidin is a toxic compound found in beetles of the genus *Epicauta* (blister beetles) that may cause vesicles or ulcers on contact with mucous membranes. Alfalfa hay contaminated with the beetles is the usual source of an outbreak. Other clinical signs are variable and dose-dependent and include tachycardia, tachypnea, fever, profuse diarrhea, stranguria, and pollakiuria. Signs of hypocalcemia, such as tremors and synchronous diaphragmatic flutter, also may occur. Complete blood count (CBC) may show hemoconcentration and neutrophilic leukocytosis. Neutropenia and leukopenia may occur in cases complicated by endotoxemia. A chemistry panel may reveal hypocalcemia, hypoalbuminemia, and elevated creatine kinase. Tentative diagnosis can be made based on history, clinical signs, and evidence of blister beetles in the alfalfa hay. Definitive diagnosis is reached through measurement of cantharidin levels in gastric contents and urine.

Mercury toxicosis also can cause oral ulceration. In one report a horse ingested an inorganic mercuric-blistering agent that was being used topically to treat dorsal metacarpal disease. Other clinical signs in this case included

edema of the ventral abdomen, distal extremities, and bulbar conjunctiva. Cases of mercury toxicosis also exhibit some form of renal dysfunction. Tetrachlorodibenzodioxin (TCDD, "dioxin") is another toxic agent that may trigger oral ulceration. Clinical signs include colic, polydipsia, anorexia, weight loss, edema, and conjunctivitis. Diagnosis is based on clinical signs and possible exposure to "dioxin"-containing industrial waste.

Uremia associated with renal insufficiency may lead to the clinical signs of uremic syndrome, which includes gingivitis and oral ulceration resulting from excess ammonia. Weight loss is the most common presenting sign in horses with chronic renal failure. Other signs include polyuria, polydipsia, anorexia, rough hair coat, and lethargy. A diagnosis of chronic renal failure is made when persistent isosthenuria (urine specific gravity 1.008-1.014) is seen with azotemia and typical clinical signs.

Adverse drug reactions may manifest as cutaneous eruptions that can result in oral ulceration. Nonsteroidal antiinflammatory drug (NSAID) toxicosis can cause oral ulceration. The ulceration can be severe and can involve the tongue, the hard palate, and the mucocutaneous junctions at the lips. Other signs include anorexia, depression, colic, diarrhea, melena, weight loss, ventral and peripheral edema (usually resulting from hypoalbuminemia), petechial hemorrhages, and ulceration of the gastrointestinal tract (stomach and right dorsal colon). Renal papillary necrosis also may occur. Diagnosis can be based on a history of chronic NSAID administration and clinical signs.

## REGULATIONS REGARDING ORAL ULCERATION

All animals that have signs of oral ulceration should be considered as potential VS cases until proven otherwise. The United States Department of Agriculture (USDA) requires all livestock with clinical signs of vesicular stomatitis to be inspected by its Animal and Plant Health Inspection Service (APHIS) foreign animal disease-trained personnel. Initially, the state veterinarian should be contacted and further investigation decided. The animal should remain in isolation, and quarantine restrictions should be undertaken until a decision is made on the disposition of the horse. Even if another diagnosis is more likely, such as a history of chronic NSAID administration, the USDA/state veterinarian should be contacted and the case discussed to ensure no potential exists for a missed diagnosis of VS.

## Supplemental Readings

- McCluskey BJ, Mumford EL: Vesicular stomatitis and other vesicular, erosive and ulcerative diseases of horses. *Vet Clin North Am Equine Pract* 2000; 16:457-469.
- Moriello KA, DeBoer DJ, Semrad SD: Diseases of the skin. In Reed SM, Bayly WM (eds): *Equine Internal Medicine*, Philadelphia, WB Saunders, 1998.
- Scott DW: Unusual immune-mediated skin diseases in the horse. *Equine Pract* 1991;13:10-18.

## CHAPTER 3.3

# Esophageal Obstruction (Choke)

NIGEL B. CAMPBELL

*Raleigh, North Carolina*

**C**hoke is the most common esophageal disorder in the horse. In most cases, it is caused by some form of intraluminal obstruction. Often clinical signs are noted immediately or soon after the horse has been fed; sometimes signs may even be observed as the horse is eating. Feed impaction (e.g., with grain, hay, pellet feeds, and beet pulp) is the most commonly diagnosed cause of choke. Other substances that may also cause choke include corn cobs, pieces of fruit or vegetables, pieces of wood, wood chips, antibiotic boluses, and a phytobezoar. The most common esophageal tumor in the horse, squamous cell carcinoma; esophageal duplication cysts; esophageal stricture; diverticulum; megaesophagus; external compression of the esophagus; or neuromuscular dysfunction can also cause obstruction. However, a history of recurrent choke normally is associated with these abnormalities. Poor dentition in older horses or erupting teeth

in younger horses result in improper mastication and predispose the horse to choke, as does being fed too soon after recovering from sedation or general anesthesia and exhaustion. The choking obstruction can occur anywhere along the esophagus, although the cervical esophagus is the most common site of impaction.

## ANATOMY

The esophagus is a musculomembranous tubular structure that originates at the pharynx and ends at the stomach. It has no digestive or absorptive functions and can be divided into three parts: cervical, thoracic, and abdominal. The main function of the esophagus is transport of the food bolus from the pharynx to the stomach. The esophagus is composed of four layers: the (1) mucosa, (2) submucosa, (3) muscularis, and (4) adventitia. The mucosal

edema of the ventral abdomen, distal extremities, and bulbar conjunctiva. Cases of mercury toxicosis also exhibit some form of renal dysfunction. Tetrachlorodibenzodioxin (TCDD, "dioxin") is another toxic agent that may trigger oral ulceration. Clinical signs include colic, polydipsia, anorexia, weight loss, edema, and conjunctivitis. Diagnosis is based on clinical signs and possible exposure to "dioxin"-containing industrial waste.

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layer consists entirely of stratified squamous epithelium. Within the submucosa are elastic fibers that contribute to the longitudinal folds of the esophagus. Striated skeletal muscle is found in the proximal two thirds of the muscularis layer, whereas the distal third consists of smooth muscle. Innervation of the esophagus is primarily from pharyngeal and esophageal branches of the vagus nerve to the striated muscle and parasympathetic fibers of the vagus nerve to the smooth muscle. Little or no innervation takes place from sympathetic fibers.

## CLINICAL SIGNS

The clinical signs of esophageal obstruction are variable. The primary clinical sign accompanying esophageal obstruction is dysphagia, signs of which include frequent or ineffective attempts to swallow, retching, intermittent flexion and extension of the neck, ptialism, coughing, and regurgitation of feed material mixed with saliva through the nostrils. If the obstruction is within the cervical esophagus, focal swelling may be seen or palpated in that region. If the swelling is also warm and painful, then cervical cellulitis may be present. Esophageal perforation may lead to palpable subcutaneous emphysema or be associated with the presence of fistulous tracts. Any horse with cervical cellulitis should be considered to potentially have an esophageal perforation and be treated accordingly. Immediate onset of clinical signs suggests an acute obstruction. A slower progression of signs or a history of recurrent choke, including weight loss, is more likely to indicate a more chronic process—such as esophageal stricture, neoplasia, or megaesophagus.

## DIAGNOSTIC PROCEDURES

### Nasogastric Intubation

The simplest way to diagnose esophageal obstruction is the inability to pass a nasogastric tube from nostril to stomach. The tube can be premeasured along the outside of the horse to obtain a rough estimate of the length of the tube required to reach the stomach. The tube should be well-lubricated and passed as smoothly as possible to prevent any further damage to the esophageal mucosa. Once the obstruction is reached, care should be taken not to try to force the tube any further to prevent esophageal perforation. Sometimes the tube can be diverted past a partial obstruction, diverticulum, stricture, or esophageal tear or perforation and will pass successfully into the stomach.

### Esophageal Endoscopy

Esophageal endoscopy enables direct observation of the obstruction. If the obstruction is in the proximal cervical esophagus, a 1-m endoscope can be used. However, for obstructions more distal, a 2- or 3-m endoscope is required. Endoscopy should be performed before any radiographic procedures that use contrast media are attempted, to enable easier viewing. Ideally, endoscopy should be performed on the nonsedated animal, but this situation is not always possible. Sedation, especially in a fractious

horse, makes passing the endoscope and carrying out the examination easier but interferes with normal esophageal motility.

As the endoscope is passed through the normally collapsed esophagus, the mucosa forms multiple longitudinal and transverse folds, which disappear during insufflation. In the thoracic esophagus, changes in intrapleural pressure during breathing may produce visible expansion and collapse of the esophageal lumen. Normal peristaltic waves causing contraction and relaxation of the lumen also may be seen. When an obstruction is found, the nature of it can be ascertained. A diverticulum may be seen as a saclike evagination of the mucosa. Reddening and thickening of the esophagus—especially the longitudinal folds—suggests esophagitis, which can cause disorders in motility that lead to obstruction. Linear mucosal ulcers, which are more severe around the entrance to the cardia of the stomach and distal esophagus, suggest reflux esophagitis. Motility disorders can be harder to diagnose, especially in the sedated animal, but may be seen as severe distention before and after insufflation and the absence of peristalsis.

Endoscopic examination after the obstruction has been relieved enables the amount of damage to the esophageal mucosa to be assessed. It may also permit easier observation of strictures and diverticula. Serial endoscopic examinations permit the assessment of mucosal healing and any subsequent stricture formation. In addition, the stomach should be assessed for signs of gastric ulceration, especially in the cardia, as this problem may contribute to reflux esophagitis.

## Esophageal Radiography

Most modern portable radiographic equipment enables radiographs to be taken of the cervical esophagus in the adult horse and possibly the complete esophagus in a foal. Radiopaque markers should be placed on the horse when each film is taken to enable films of the same area to be taken again, such as after introduction of contrast media. The normal esophagus may not be visible on survey films. However, small amounts of intraluminal air may be visible. Larger amounts of intraluminal air suggest a motility disorder. Subcutaneous emphysema will be noted if an esophageal perforation is present.

Esophageal obstruction or choke after the ingestion of feed can have a variable appearance on radiographs. Usually, a mottled gas and soft tissue opacity results from the mixture of gas and food (Figure 3.3-1). Air is visible within the opacity or at one or both ends of the obstruction. Usually the opacity is oval in shape. Feed material may also demonstrate a dense, granular pattern appearance on radiographs.

Contrast radiography also can be used to assess the esophagus (Figure 3.3-2). If esophageal perforation is suspected, then a contrast study should not be performed. Most intraluminal obstructions are visible on survey films, but the use of a contrast media may help in some cases. Usually, contrast radiography is used once the obstruction is cleared to help ascertain the cause of obstruction. Barium paste is used to evaluate the esophageal mucosa because it coats the mucosa for several minutes, permitting





**Figure 3.3-1** Survey radiograph of the cervical region of a horse. Note the mottled opacity indicating an esophageal obstruction (*arrow*) with evidence of gas density within the soft tissues as a result of esophageal rupture.



**Figure 3.3-2** Contrast radiograph of the esophagus in a horse after correction of esophageal obstruction. Note the outline of a diverticulum (*arrow*) that became impacted with feed material, initiating the obstruction.

easier identification of strictures. Contrast medium in the normal esophagus forms fine radiographic linear streaking by lining the longitudinal folds of the esophagus. If megaesophagus or diverticula are thought to be the cause of choke, barium suspension is the contrast medium of choice. The suspension provides a greater volume of contrast medium, which more easily outlines diverticula and dilatations of the esophagus. The liquid barium can be given by mouth or via a nasogastric tube to help prevent possible aspiration of contrast medium, especially if a pharyngeal dysfunction is present.

Contrast radiography should be performed on a non-sedated horse to help maintain normal esophageal motility. However, this situation is not always possible. Interpretation of esophageal contrast studies on sedated horses can be difficult because delayed esophageal emptying and esophageal distention with air and contrast medium have been associated with the use of sedatives in the horse. These artifacts may also occur with the passage of a nasogastric tube. In this author's opinion the risk of aspiration outweighs the formation of these artifacts, and a nasogastric tube should be used to administer the contrast medium.

Esophageal strictures usually have a smooth wall, with retention of contrast medium cranial to the stricture and dilation of the esophagus distal to the stricture. Because esophageal spasm may be interpreted as a stricture, a second radiograph of the area should be taken to differentiate between the two and ensure that the abnormality is still present. External compression of the esophagus by adjacent tissue, such as a neoplasm, can be seen as the esophagus appearing to deviate around a mass. In addition, a narrowed path also may be outlined by contrast medium. Esophageal neoplasms are rare in the horse. However, if a mass is seen and the mucosal surface of the esophagus demonstrates irregularity, neoplasia should be considered on the list of differential diagnoses along with abscessation.

Mixing a contrast medium with feed enables a more accurate evaluation of the esophageal transit of a food bolus. The normal transit time for a bolus is 4 to 10 seconds. If the food bolus appears to have moved minimally when serial radiographs are taken, then impaired esophageal transit can be diagnosed. Causes include focal esophagitis and motility disorders.

Double contrast studies of the esophagus also may be performed and involve insufflation of the esophagus via a nasogastric tube after the contrast medium is administered. This step may help more effectively outline abnormalities of the esophagus, especially mucosal lesions and small neoplasms. Megaesophagus may occur focally if it is secondary to a stricture or may involve the entire esophagus if it is due to neuromuscular dysfunction or an abnormality of the cardiac sphincter. The affected segment of the esophagus may be dilated with fluid, gas, food, or a combination of the three. Pulsion diverticula are seen as rounded outpouchings of the esophagus, with normal-appearing esophagus proximally and distally, and can be of varying sizes. These are formed by herniation of esophageal mucosa through an acquired defect in the muscularis layer of the esophagus. Traction diverticula have a more pointed appearance. They are much smaller and of little significance and are formed when traction exists on the esophageal wall due to a periesophageal scar.

### Esophageal Ultrasound

Ultrasound is best used to evaluate the cervical esophagus. During ultrasound examination the esophagus is most easily identified in the midportion of the neck between the trachea and the left carotid artery. Once identified, the esophagus can be followed proximally and distally. The esophageal lumen is irregular to star-shaped and is hypoechoic. The serosa is hypoechoic, and the wall is usually 3 to 4 mm thick.

Esophageal obstruction due to feed impaction is seen as a heterogenous echogenic mass causing dilation of the lumen. A foreign body, such as a piece of wood, may cast strong acoustic shadows, making them easier to identify. Narrowing of the esophageal lumen associated with stricture formation also can be noted. Esophageal diverticula distended with saliva, food, fluid, or air can be detected via ultrasound but are difficult to identify if they are empty. A dilated esophagus is easily visualized with ultrasound because of its increase in lumen diameter and air/fluid contents. Esophageal rupture with subsequent cellulitis can also be visualized via ultrasound. However, the actual site of perforation is unlikely to be identified. Cellulitis is seen as bright, hyperechoic echoes, which represent free gas. Thickening of the esophageal wall also may be appreciated by ultrasonography and can indicate an ongoing esophagitis.

## TREATMENT

Some esophageal obstructions may resolve spontaneously and require no additional therapy. Once the episode of obstruction has begun, the horse should be placed in an empty stall containing no food, water, or bedding until treatment is begun. Initial treatment requires relaxation of the esophageal musculature and lowering of the horse's head to allow saliva and food to pass from the nostrils and minimize the possibility of aspiration; this position is achieved by sedation with xylazine or detomidine hydrochloride and acepromazine in combination. An oral examination may reveal poor dentition or a foreign body. Some foreign bodies may be amenable to endoscopic removal with "grab" forceps or a snare. If a pharyngeal foreign body is causing the obstruction, it may be able to be removed manually with the aid of a full-mouth speculum. However, such removal is best achieved under general anesthesia. If the oral cavity is clear and no obvious pharyngeal obstruction is present, a nasogastric tube then is passed into the esophagus. Small feed impactions may be pushed into the stomach, but care must be taken not to exert too much pressure and cause a possible perforation.

If the impaction is not easily relieved then this author administers lidocaine (50-100 ml, depending on size of animal; 27% solution) through either the nasogastric tube or an endoscope at the site of impaction. The mechanism of action of lidocaine is not known, but the hypothesis is that the lidocaine relieves esophageal spasm, permitting the esophageal musculature to relax. A recent study evaluating the effect of oxytocin on esophageal pressure showed that when administered at 0.11 to 0.22 IU/kg via intravenous (IV) injection, short-term esophageal relaxation occurred. Greater relaxation likely occurs in the proximal esophagus (striated muscle) than in the distal esophagus (smooth muscle). An *in vitro* study researching the effect of drugs on isolated strips of striated muscle and smooth muscle from the esophagus showed that oxytocin, acepromazine, and to a lesser extent xylazine cause relaxation of the distal equine esophagus. This author has had some success using oxytocin for cases of choke involving the proximal esophagus.

Approximately 10 to 20 minutes after drugs are administered to relax the esophagus, a nasogastric tube is

passed to the site of the impaction and gentle lavage with warm water begun. Water for lavage of the esophageal obstruction can be administered by gravity through the nasogastric tube via a funnel; in other cases a stomach pump can be used. The risk of causing esophageal perforation is lessened by use of gravity as less pressure is created. However, the gravity method may require the added pressure of water being pumped in to clear the obstruction. The method of administration must be decided on a case-to-case basis. Water containing food particles should be seen coming back through the tube and from the nostrils. Relieving the spasm also may provide some analgesia.

If gentle lavage is not successful at relieving the obstruction, more vigorous lavage is required, a process that can be achieved in two ways. A cuffed nasogastric tube can be placed at the obstruction site and the cuff inflated, or a cuffed endotracheal tube can be passed into the proximal esophagus, the cuff inflated, and a nasogastric tube subsequently passed through the endotracheal tube to the site of the obstruction. Another dose of lidocaine may be used at this point. A more vigorous lavage using large volumes of warm water then can be performed in an attempt to relieve the obstruction. This more vigorous lavage also can be attempted under general anesthesia with an additional cuffed endotracheal tube in the trachea, thereby minimizing the chance of aspiration. Mineral oil or dioctyl sodium sulfosuccinate (DSS) should not be used at any time during a lavage procedure due to the severe damage that may occur if the horse aspirates these substances.

If an obstruction in the cervical esophagus cannot be relieved, an esophagotomy can be performed to remove the obstruction. IV fluids should be provided in cases complicated by dehydration. Oral fluids should be allowed only after removal of the obstruction in cases in which the pharyngeal/esophageal inflammation is resolving. One of the main complications of esophageal obstruction is pneumonia from aspiration of food, saliva, or esophageal lavage fluid. All horses should be placed on prophylactic broad-spectrum antibiotics—initially IV or intramuscular (IM) rather than orally, the latter of which may worsen the condition. The other main complication is stricture formation at the site of the original obstruction. Predicting which cases will develop strictures is difficult, but the more severe the mucosal damage, the more likely strictures are to form. The prevention of stricture formation is based on the control of esophageal inflammation by use of nonsteroidal antiinflammatory drugs (NSAIDs) and the ability to feed the horse orally, even in small amounts, to try to stop the esophagus from narrowing.

NSAIDs should be used to control pain and inflammation. If gastric ulceration is present, treatment should consist of an H<sub>2</sub>-antagonist or omeprazole. Omeprazole is the drug of choice in this situation. Sucralfate also may be used. Horses that have had simple obstructions relieved with only mild or no mucosal damage can be fed after 12 to 24 hours, with small amounts of a pellet gruel or grass every 4 to 6 hours initially. The amount can be increased as the condition improves. No hay should be fed for at least 4 to 5 days, and then hay can be gradually introduced.

For animals that have had more complicated and/or prolonged obstructions with moderate-to-severe mucosal damage, feed should not be provided for at least 48 to

72 hours. In some cases the horse may need to be fed via a nasogastric tube or require partial or total parenteral nutrition until the mucosa has healed enough to tolerate oral feedings. Use of a nasogastric tube in a minority of cases may slow mucosal healing or even exacerbate the damage, but if access to parenteral nutrition is not available, the tube may be the only available way to provide the horse with adequate nutrition. Hay should not be fed for at least 7 to 10 days. Ideally, mucosal healing should be monitored endoscopically to assess when to begin to feed the horse and to note the formation of any strictures at the obstruction site. A nasogastric tube can be placed distal to a still-present obstruction or to a severely damaged esophageal mucosa or perforation through an esophagotomy to provide adequate nutrition. However, this procedure is only a temporary measure and cannot be used indefinitely. In the case of esophageal perforations, this method permits the perforation to heal by second intention.

### PREVENTION

Esophageal obstruction is difficult to prevent. In some cases, horses "bolting" food can cause choke, an incidence

that occurs when a number of horses are fed together and compete for food. To prevent "bolting," the horses should be fed separately, away from the other horses. Large objects (those too large to ingest) also may be placed in the feed bowl so that the horse has to search for the food around the objects, thus slowing down its speed of eating. Because choke also may be caused by certain feedstuffs in some horses, avoidance of these should minimize the chance of a recurrent episode of choke.

### Supplemental Readings

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## CHAPTER 3.4

# Gastric Ulcer Syndrome

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**E**quine gastric ulcer syndrome (EGUS) is a complicated and multifactorial problem that has a prevalence ranging from 25% to 51% in foals and 60% to 90% in adult horses, depending on signalment, coexisting clinical disorders, performance level, and location of the ulcer within the stomach.

### PATHOGENESIS

EGUS in foals and horses is due to an imbalance between mucosal aggressive factors (hydrochloric acid, pepsin, bile acids, and organic acids) and mucosal protective factors (bicarbonate, mucus). Because the glandular mucosa has more protective factors than the nonglandular mucosa, the glandular mucosa may have different causes for ulceration. The mucus-bicarbonate layer covers the surface of the glandular

mucosa. Prostaglandin  $E_2$  promotes secretion of this layer and enhances mucosal blood flow, mucus, and bicarbonate production. Thus inhibiting prostaglandin synthesis decreases mucosal blood flow and mucus and bicarbonate secretion and increases gastric acid secretion by the glandular mucosa. In addition, prostaglandins may help maintain the integrity of the nonglandular and glandular mucosa by stimulation of production of surface-active protective phospholipids, enhancement of mucosal repair, and prevention of cell swelling by stimulation of sodium transport. Stress resulting from parturition in foals or the stress of training and confinement in adult horses may lead to the release of excess endogenous corticosteroids, which can inhibit prostaglandin synthesis. This decrease in prostaglandins may lead to breakdown of mucosal protective factors.

Glandular mucosal ulceration requires exposure to acid but probably also relates to concurrent failure or disruption of mucosal protective factors. Nonsteroidal antiinflammatory drugs (NSAIDs) may be involved in the latter mechanism. NSAIDs result in ulceration of glandular and squamous mucosa in foals, and gastric mucosal damage

72 hours. In some cases the horse may need to be fed via a nasogastric tube or require partial or total parenteral nutrition until the mucosa has healed enough to tolerate oral feedings. Use of a nasogastric tube in a minority of cases may slow mucosal healing or even exacerbate the damage, but if access to parenteral nutrition is not available, the tube may be the only available way to provide the horse with adequate nutrition. Hay should not be fed for at least 7 to 10 days. Ideally, mucosal healing should be monitored endoscopically to assess when to begin to feed the horse and to note the formation of any strictures at the obstruction site. A nasogastric tube can be placed distal to a still-present obstruction or to a severely damaged esophageal mucosa or perforation through an esophagotomy to provide adequate nutrition. However, this procedure is only a temporary measure and cannot be used indefinitely. In the case of esophageal perforations, this method permits the perforation to heal by second intention.

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### PATHOGENESIS

EGUS in foals and horses is due to an imbalance between mucosal aggressive factors (hydrochloric acid, pepsin, bile acids, and organic acids) and mucosal protective factors (bicarbonate, mucus). Because the glandular mucosa has more protective factors than the nonglandular mucosa, the glandular mucosa may have different causes for ulceration. The mucus-bicarbonate layer covers the surface of the glandular

mucosa. Prostaglandin  $E_2$  promotes secretion of this layer and enhances mucosal blood flow, mucus, and bicarbonate production. Thus inhibiting prostaglandin synthesis decreases mucosal blood flow and mucus and bicarbonate secretion and increases gastric acid secretion by the glandular mucosa. In addition, prostaglandins may help maintain the integrity of the nonglandular and glandular mucosa by stimulation of production of surface-active protective phospholipids, enhancement of mucosal repair, and prevention of cell swelling by stimulation of sodium transport. Stress resulting from parturition in foals or the stress of training and confinement in adult horses may lead to the release of excess endogenous corticosteroids, which can inhibit prostaglandin synthesis. This decrease in prostaglandins may lead to breakdown of mucosal protective factors.

Glandular mucosal ulceration requires exposure to acid but probably also relates to concurrent failure or disruption of mucosal protective factors. Nonsteroidal antiinflammatory drugs (NSAIDs) may be involved in the latter mechanism. NSAIDs result in ulceration of glandular and squamous mucosa in foals, and gastric mucosal damage

was found at necropsy in six of eight mature horses given large doses of phenylbutazone. NSAIDs inhibit cyclooxygenase, which in turn inhibits prostaglandin  $E_2$  production, thereby resulting in increased acid secretion, decreased mucosal blood flow, and disruption of the mucus-bicarbonate barrier. One study of Southern California racehorses showed no correlation between the use of NSAIDs and gastric ulceration; however, the ulcers in these racehorses were located primarily in the nonglandular region, which may be caused by a different mechanism. Interestingly, a correlation existed between the use of furosemide and reduced gastric ulceration, possibly as a result of positive effects on gastric vasculature. Therefore the degree of gastric blood flow may play a central role in glandular gastric ulceration.

Ulcers in the nonglandular mucosa primarily are due to prolonged exposure to hydrochloric acid (HCl), pepsin, bile acids, and organic acids (e.g., volatile fatty acids [VFA])—similar to gastroesophageal reflux disease (GERD) in humans. Excessive exposure to HCl and to a lesser extent, VFAs (acetic, butyric, propionic, and valeric acids), may be the primary cause of nonglandular mucosal ulceration. The nonglandular mucosa has no mucous layer and responds to acid irritation by increasing the thickness of its keratin layer, which provides only minimal protection from acid and pepsin. Gastric lesion formation also may be related to desquamation of the stratified squamous epithelium of the stomach because replacement of desquamated epithelium seems to be delayed in foals. Stomach pH has been implicated strongly in gastric ulceration in adult horses. In one study the squamous epithelium had a lower pH than the glandular mucosa, with the lowest readings near the margo plicatus, where most ulcers naturally occur. Approximately 50% of the horses with moderate to severe ulceration demonstrated a significantly lower stomach pH than those horses with mild or no ulceration.

Similar studies in foals showed no difference in the mucosal surface pH in the same region of the stomach in foals with or without lesions. However, lower gastric fluid pH values were found in recumbent foals and those that nursed infrequently, suggesting that milk buffers gastric acid, whereas recumbency may lead to increased exposure of the nonglandular mucosa to acid. Delayed gastric emptying or decreased gastric motility also may be contributory in neonatal foals with concurrent disease or gastric outflow obstruction.

Organic acids may act synergistically with HCl to cause EGUS in horses. For example, VFAs or short-chain fatty acids produced as byproducts of carbohydrate fermentation have been found to induce injury to the nonglandular mucosa of the equine stomach in the presence of a low pH. This finding is due to VFAs that become undissociated at low pH and are able to penetrate nonglandular epithelial cells, resulting in acidification, cell swelling, inflammation, and ulceration. In the equine stomach, VFAs have been found to be present in sufficient quantities to lead to acid injury. Because performance horses consume diets high in fermentable carbohydrates, VFAs generated by resident bacteria may cause acid injury and ulceration in the nonglandular mucosa. Bile salts from duodenal reflux and pepsin have been implicated in gastric ulcer disease in

other species and possibly the horse. Bile acids increase the permeability of the nonglandular mucosa to hydrogen ions, thereby acting synergistically with acid to cause mucosal ulceration.

Feed deprivation has been found to be a cause of nonglandular ulceration resulting from repeated exposure of the nonglandular mucosa to high acidity. For instance, horses fed hay continuously had higher median 24-hour gastric juice pH (3.1) compared with fasted horses (1.6). In addition, the type of roughage and timing of feeding may be contributory factors to gastric ulceration. In one study, horses fed alfalfa hay had significantly higher gastric juice pH and lower gastric ulcer scores compared with horses fed brome grass hay. It has been postulated that alfalfa hay might have a protective effect on the mucosa because of its calcium and/or protein concentrations. In general, high-roughage diets have been found to stimulate bicarbonate-rich saliva production, which may buffer gastric acid.

*Helicobacter pylori* is considered to be the primary cause of peptic ulcers in humans, but this organism has not been found in the horse. However, in a recent study, *Helicobacter*-specific DNA was isolated from the glandular and squamous epithelia of seven horse stomachs, including two horses with squamous erosions and one horse with glandular epithelial erosions. This study suggests that *Helicobacter* spp. may be involved in the etiology of EGUS. Many other types of bacteria have been associated with lesions in the horse, but none appear to be pathogenic.

Stress has been implicated as a cause of gastric ulcers. For example, 35% of foals in one study that were stressed because of concurrent clinical illness had glandular gastric ulceration. A greater prevalence and severity of gastric lesions also has been found in adult horses in training, possibly because of the stressful effect of strenuous exercise. Exercise could cause gastric ulceration by delaying gastric emptying and/or increasing gastric acid secretion. In Southern California, 81% of racehorses in active training had gastric ulcers, and poor performance was correlated with increasing ulcer severity. Of 67 Thoroughbred racehorses examined gastroscopically at a Maryland racetrack, 93% had one or more lesions present in the gastric mucosa. Also, in a recent study in Standardbred racehorses in Quebec, Canada, 63% of Standardbred racehorses in active race training had gastric ulcers.

## CLINICAL SYNDROMES

### Gastric Ulceration in Foals

Foals of all ages can be affected by gastric ulcer disease. Four separate clinical syndromes have been recognized in foals: silent (subclinical) ulcers; active (clinical) ulcers; perforating ulcers with diffuse peritonitis; and pyloric strictures from resolving ulcers, which may result in gastric outflow obstruction. Probably the most common syndrome in foals is clinically inapparent, or silent gastric, ulceration. These ulcers usually are found in the nonglandular mucosa along the greater curvature adjacent to the margo plicatus but also may be found in the glandular mucosa. These types of ulcers are commonly seen in foals younger than 4 months. Subclinical ulcers may heal

without treatment and may be found incidentally at necropsy.

Active ulcers usually occur in foals 270 days of age or younger. These ulcers are found primarily in the nonglandular mucosa along the greater or lesser curvature next to the margo plicatus or in the glandular mucosa. Clinical signs result when gastric ulcers become larger and more diffuse and coalesce. Diarrhea and poor appetite are the most frequent clinical signs found in these foals. Poor growth, rough hair coat, potbellied appearance, bruxism, dorsal recumbency, excessive salivation, interrupted suckling, and colic also may be observed. Foals with large ulcers exhibit severe signs of colic, tend to roll, lie in dorsal recumbency, and may be sensitive to abdominal palpation just caudal to the xiphoid process. These signs may be due to gastric distention and gastroesophageal reflux.

Perforating gastric ulcers are uncommon but can occur in the nonglandular mucosa (most frequently) and glandular mucosa of the stomach or in the duodenum of foals. This type of ulcer may result in diffuse peritonitis, which is almost always fatal. Clinical signs are often absent until directly before rupture. After gastric rupture, foals show progressive evidence of endotoxemia and may have abdominal distention and colic. Foals considered to be at high risk should be treated prophylactically to prevent gastric rupture.

Pyloric or duodenal ulcers are uncommon in foals and may produce stricture and gastric outflow obstruction as they resolve. This type of ulcer syndrome can affect foals of all ages, but foals 3 to 5 months of age tend to be more susceptible. Clinical signs may not be seen in foals with duodenal or pyloric ulcers, but if such signs do develop, they are usually related to gastric outflow obstruction. Clinical signs of gastric outflow obstruction include bruxism, drooling of milk, excess salivation, low-volume diarrhea, postprandial colic, and scant feces. The foals may have aspiration pneumonia, cholangitis, erosive esophagitis, GERD, and severe gastric ulceration. In severe cases, dehydration and systemic hypochloremic metabolic alkalosis may result because of duodenal strictures and outflow obstruction.

### Gastric Ulceration in Yearlings and Mature Horses

Clinical syndromes of gastric ulceration in yearling and mature horses are more economically significant but less well-recognized. Silent or nonclinical ulcers are probably most common, but clinical gastric ulcers, duodenal ulcers, duodenal stricture, erosive esophagitis, and gastric rupture also may occur. Gastric ulcers are found primarily in the nonglandular mucosa adjacent to the margo plicatus along the greater and lesser curvature. Glandular ulcers are found less often in yearling and mature horses than in foals. Glandular ulcers are frequently associated with the administration of NSAIDs in yearling and mature horses. Mild multifocal gastric ulceration of the nonglandular mucosa usually is seen in yearlings and 2-year-olds in training without the production of clinical signs. Horses in this age group may not show clinical signs, even when ulceration is severe. Important risk factors for ulceration in this age group include training, stress of concurrent disease, and NSAID administration. Signs in horses with EGUS in-

clude acute and recurring colic, poor body condition, partial anorexia, poor performance, poor appetite, and attitude changes. Gastric ulcers are consistently more severe in horses with clinical signs, compared with horses without clinical signs, and may be the primary cause of colic or may be secondary to other gastrointestinal tract problems. Frequently no correlation exists between clinical signs and gastric ulcer severity, as detected by endoscopy.

### DIAGNOSIS

Diagnosis of gastric ulcer disease is based on clinical signs, endoscopic examination, and response to treatment. Clinical signs include bruxism (grinding of teeth), ptyalism (excessive salivation), colic, poor performance, gastric reflux, depression, lack of appetite, and abdominal pain (sometimes resulting in dorsal recumbency).

Endoscopic examination is required to confirm the presence of gastric ulcers, determine the location and severity of the lesions, and analyze treatment response. A 2-m endoscope is needed for gastroscopy in the adult horse. However, a 110- to 140-cm endoscope may be sufficient for use in foals 30 to 40 days of age. The endoscope is inserted through the nasal passages, down the esophagus, and into the stomach. The stomach is insufflated with air, and the glandular and nonglandular regions of the stomach are evaluated for gastric lesions.

Gastric lesions are found primarily along the margo plicatus of the stomach in the squamous mucosa. In foals 60 days of age or younger, lesions are observed most commonly in the stratified squamous epithelium adjacent to the margo plicatus rather than in the glandular mucosa. Lesions sometimes occur in the glandular mucosa in foals with other clinical disorders, such as rotavirus-induced diarrhea or septicemia. In older foals, lesions are more prevalent along the margo plicatus and the lesser curvature in the squamous mucosa, possibly due to increased maturity in mucosal protective factors in the glandular mucosa in older horses.

### TREATMENT

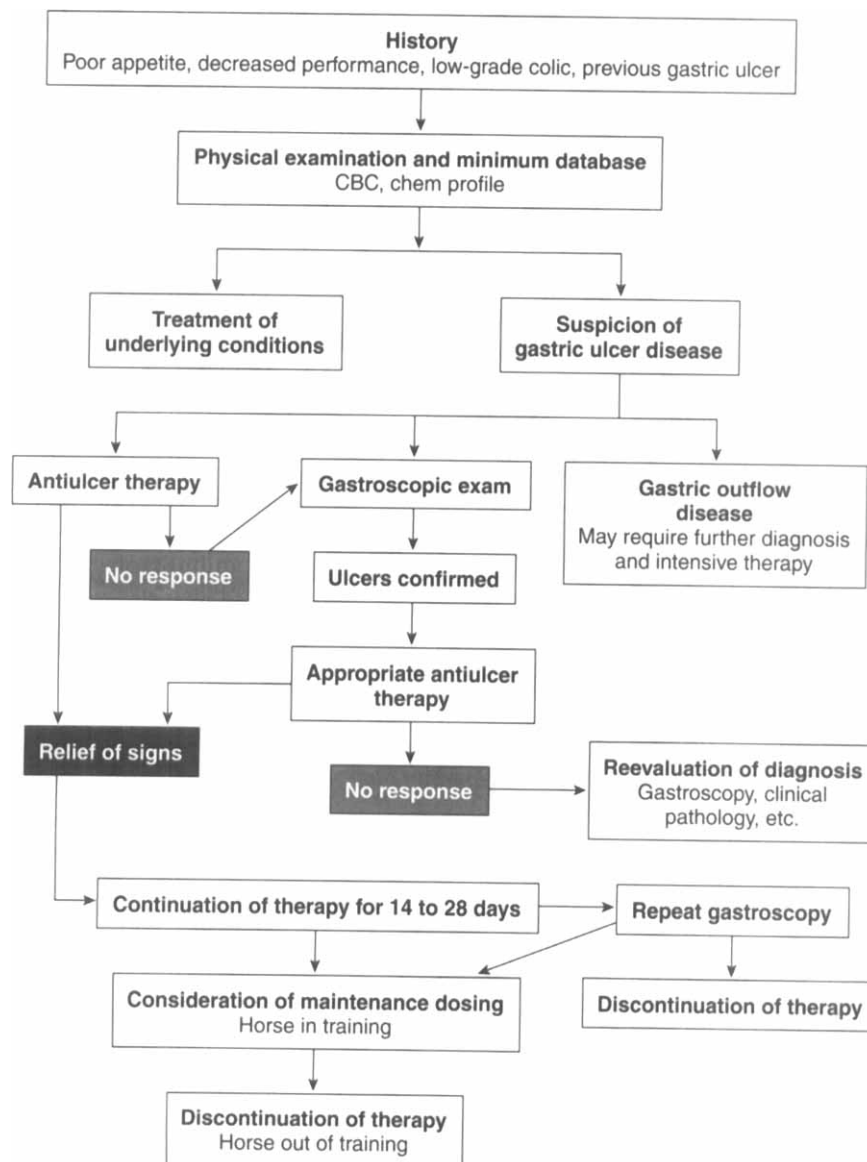
Several types of agents are available to treat gastric ulcers in horses. These include antacids,  $H_2$ -receptor antagonists, sucralfate, prostaglandin analogues, and omeprazole. These treatments act by differing mechanisms and agents, and dosages for horses are listed in Table 3.4-1. The protocol for treatment of ulcers is shown in Figure 3.4-1.

Antacids, including nutraceuticals, have not yet been determined to be effective in the treatment of gastric ulcers. They can be used to ameliorate clinical signs or perhaps to help prevent gastric ulcer recurrence after successful treatment with an  $H_2$  antagonist. Types of antacids include aluminum hydroxide, magnesium hydroxide, and calcium carbonate. Most are mixtures of aluminum hydroxide and magnesium hydroxide. Magnesium salts and calcium carbonate act rapidly to neutralize acid but do not have a long duration of effectiveness. For example, a dose of 180 ml of an aluminum/magnesium hydroxide combination (Maalox) increases the pH of gastric fluid to greater than 3.0 for 15 to 30 minutes in the horse. Thus 200 to 250 ml of an aluminum/magnesium hydroxide contain-

**Table 3.4-1**  
**Therapeutic Agents Commonly Used to Treat Gastric Ulcers**

Drug	Dosage (mg/kg/bwt)	Dosing Interval	Route of Administration
ranitidine	6.6	q6-8h	PO
	1.5	q6-8h	IV, IM
cimetidine	20-25	q6-8h	PO
omeprazole	4	q24h	PO
	0.5	q24h	IV
sucralfate	20-40	q8h	PO
Al/Mg hydroxide	0.5 ml/kg	q4-6h	PO
prostaglandin analogues	1-4 µg	q24h	PO

PO, By mouth; q6-8h, every 6 to 8 hours; IV, intravenous; IM, intramuscular.



**Figure 3.4-1** Flow sheet for treatment of equine gastric ulcer disease (EGUS). CBC, Complete blood count. (Modified from Pipers FS: Recommendations for diagnosis and treatment of equine gastric ulcer syndrome [EGUS]. Equine Vet Educ 1999; 1(2):122-134.)

ing antacid administered orally 3 to 6 times daily may help prevent the return of clinical signs but is probably not effective in healing gastric ulcers.

The H<sub>2</sub>-receptor antagonists suppress HCl secretion by binding and competitively inhibiting the parietal cell histamine H<sub>2</sub> receptor. Activation of this receptor normally activates adenylate cyclase to produce cyclic adenosine monophosphate (cAMP). Treatment with H<sub>2</sub>-receptor antagonist in 55 horses with gastric ulceration led to endoscopically confirmed resolution of lesions or improvement in 32 horses. Ranitidine (Zantac) and cimetidine (Tagamet) are two drugs of this type used in the horse. These drugs have helped to resolve gastric lesions in foals and adult horses. The dosage of ranitidine is usually 6.6 mg/kg every 8 hours. Ranitidine is available as syrup and in the liquid and injectable forms. Of 32 horses treated with ranitidine, 16 experienced significant improvement in gastric lesion scores and complete healing. However, no untreated controls were included in the study. Cimetidine is not as potent as ranitidine and should be given at a maximum dosage of 25 mg/kg every 6 to 8 hours. Cimetidine is available in tablet, liquid, and injectable forms and may be administered intravenously or intramuscularly at 6.6 mg/kg every 6 hours. Lower doses can relieve the discomfort of ulcers but are not effective in healing gastric ulcers. Therapy should continue for 14 to 21 days. Healing time varies depending on the individual horse.

Sucralfate (Carafate) is a sulfated polysaccharide, which is a combination of octasulfate and aluminum hydroxide. Its mechanism of action involves adhering to ulcerated mucosa, forming a proteinaceous bandage, and stimulating increased prostaglandin E<sub>1</sub> synthesis and mucus secretion. Sucralfate may best be used in addition to H<sub>2</sub> antagonist treatment to aggressively suppress acid secretion in addition to increasing mucosal protective factors. It is available in tablet form and is used at a dose of 20 to 40 mg/kg every 8 hours. It also inactivates pepsin and adsorbs bile acids. However, in a study that compared sucralfate (22.0 mg/kg PO) to corn syrup for 14 days, sucralfate did not promote greater healing than corn syrup.

Prostaglandin analogues, primarily synthetic prostaglandin E<sub>2</sub> (Cytotec), have been used to treat EGUS. These drugs enhance mucosal protection by stimulating mucus and bicarbonate production and may aid in the treatment and prevention of gastric ulcers induced by NSAIDs. Reported side effects of synthetic prostaglandin administra-

tion in humans include abdominal pain, diarrhea, bloating, and cramping. These side effects also may occur in horses. A dose of Cytotec of 1 to 4 µg/kg body weight (bwt) orally once daily has been reported to significantly reduce free acid in the stomach of horses.

Omeprazole, a substituted benzimidazole and a proton pump inhibitor, acts by blocking secretion of H<sup>+</sup> at the parietal cell membrane H<sup>+</sup>/K<sup>+</sup> ATPase pump (proton pump). Omeprazole binds irreversibly with this enzyme, which may explain its long-term blockade of acid secretion. Omeprazole acts to completely suppress acid secretion, and its effects can last up to 27 hours in horses depending on the dose. A dose of 0.5 mg/kg intravenously decreases gastric acid secretion by greater than 90% within 30 minutes and is associated with significant healing of gastric ulcers in horses administered NSAIDs. Omeprazole paste (4.0 mg/kg; GastroGard) given orally once daily to horses in active race training causes significant improvement (>90%) in gastric ulcer scores and healing (77%), compared with sham-dosed horses. Omeprazole paste prevents recurrence of gastric ulcers when given at full and half-doses. GastroGard remains the only FDA-approved treatment for EGUS and is labeled for treatment and prevention of recurrence of EGUS. The current recommendation for treatment of EGUS is 4 mg/kg orally once daily and for prevention of recurrence is 2.0 mg/kg orally once daily.

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## CHAPTER 3.5

# Management Factors Associated with Colic

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A number of management factors that predispose horses to colic can be altered to reduce the risk of this problem. Many veterinarians assume that horse owners are familiar with horse management to prevent health problems. This assumption may be misguided; much of the information about feeding and caring for horses is anecdotal and empiric, and some common beliefs are either incorrect or unsubstantiated by epidemiologic studies. In addition, because the average duration of horse ownership in the United States has been estimated at approximately 5 years, new horse owners are always abundant. Many new horse owners are unfamiliar with the best way to manage their horses to prevent health problems. Consequently, veterinarians must be prepared to advise clients with horses about management factors that predispose to colic. Horses with histories of previous colic are at increased risk of developing colic again, so their owners must be prepared.

The exigencies associated with treatment of horses with colic often result in failure to obtain a careful history for the affected horse. A history may reveal predisposing factors for colic that could be altered to prevent recurrence of the problem. Medical history for horses with colic should include information about management, particularly with respect to diet, stabling/housing, and activity because changes in these factors seem to predispose horses particularly to developing colic.

The few epidemiologic studies of the association of management practices with equine colic have often yielded conflicting results. The sources of conflict include differences among studies in design and populations studied. Those findings consistent among studies are most likely to be generally applicable to all groups of horses. The purpose of this chapter is to summarize current knowledge of management factors that have been associated with colic.

### DIET AND FEEDING

Change in diet, specifically changes in the batch, type, or amount of hay and in the type or amount of concentrate, is associated with increased risk of colic.

Evidence associating a specific type or amount of concentrate with colic is conflicting. Feeding whole grain corn was associated with increased colic in one study, whereas feeding other whole grains was associated with colic in a second study. Other studies have failed to identify an association between type of concentrate and colic. Some re-

ports have documented that increased amount of concentrate enhances the risk of colic. In summary, a wide variety of concentrates can be safely fed to horses, but increased risk of colic should be expected when large amounts of any concentrate are fed.

Feeding alfalfa hay is associated with increased risk of enterolithiasis. Although not substantiated by a controlled study, feeding coastal grass hay is regarded as a risk factor for ileal impactions in the United States. In Texas, feeding hays other than coastal or Bermuda grass is associated with colic. Although the cause of the associations has not been determined, it is plausible that these other hays have higher fiber contents and decreased digestibility relative to coastal and Bermuda grass or alfalfa hay, thereby predisposing to colic. Feeding round bales of hay is associated with colic. Higher fiber content of the hay and exposure to outdoor elements such as rain may account for decreased digestibility or quality (e.g., moldiness) of round-bale hay.

Increased time at pasture is associated with decreased risk of colic and may be attributable to the salutary effects of constant grazing and avoidance of the adverse physiologic sequelae of feeding concentrates twice daily (that is, fluid, electrolyte, and pH changes in the hindgut). However, horses at pasture may be less frequently observed, and milder episodes of colic may not be detected. Turnout of horses onto lush pasture may even predispose to colic, and changing pastures also may be associated with colic.

### STABLING AND HOUSING PRACTICES

Increased time being stalled is a risk factor for impaction of the large colon. Because lack of access to adequate fresh water is a risk factor for colic, horse owners and caregivers should be reminded about the importance of regularly cleaning and refilling water buckets and troughs to provide access to fresh water. When water consumption may be decreased relative to needs (for example, decreased consumption during cold weather or increased fluid losses during transport or during competition in hot, humid weather), providing salt or flavoring to encourage horses to drink may be beneficial. Salt can be provided as a block or top-dressed on feed.

### ACTIVITY

A number of studies have documented that both increases and decreases in activity levels may be associated with

colic. Associations of a particular activity with colic have been inconsistent, but individual studies have associated racing, eventing, showing, and breeding with increased risk of colic. Generally, intensive exercise has been associated with increased risk of colic. Broodmares, particularly periparturient mares, are at increased risk of large colon volvulus.

Changes in activity often occur concomitantly with changes in stabling and diet. For example, a horse with a lameness problem might simultaneously have its exercise curtailed, be restricted to a stall, and experience a change in diet. Epidemiologically, this concurrence can make it difficult to separate the effects of activity from those of stabling, diet, or both. Clinically, colic is multifactorial, and no single risk factor is likely to completely explain any given episode of the problem.

### VETERINARY HEALTH MANAGEMENT

Regular administration of an anthelmintic, rather than infrequent purging of parasites, appears to decrease the risk of colic. Conflicting results (increased risk, decreased risk, and no difference) also exist for the association of recent administration of an anthelmintic and colic. Because more than one study has reported increased risk of colic in association with recent administration of an anthelmintic, some risk may be associated with anthelmintic administration. However, this association possibly is biased by owners or veterinarians being more likely to recall or record a history of anthelmintic administration for horses that experience colic (so-called recall bias).

Epidemiologic evidence that a particular anthelmintic is associated with colic is lacking, although products that result in rapid killing of adult stages would be expected to predispose to intractable ascarid impactions in heavily parasitized young horses. Evidence that daily administration of pyrantel tartrate decreases the risk of colic is conflicting: one study demonstrated a lower risk of colic among treated horses, but others have failed to detect a significant difference in risk of colic among horses treated daily as compared with those treated periodically (i.e., purged). In the United Kingdom, strong evidence exists that tapeworms are associated with ileal impactions and other forms of colic. Similar studies have not been conducted in the United States, but it seems advisable to design anthelmintic programs for horses to target tapeworms, regardless of region.

Dental disorders have been anecdotally incriminated as predisposing to colic. To date, epidemiologic studies have not documented an association between dental care and colic, and a study designed to specifically address the association of dental disorders with colic has not been reported. It seems plausible that regular dental care may decrease the risk of some types of colic (e.g., esophageal obstruction and impaction of the large colon).

### SUMMARY

Causes of colic are multiple, and their interrelationship is often complex. The effects of a given factor associated with colic must always be interpreted in light of its association with other factors that increase the risk of colic. For example, the increased risk of colic among Thoroughbred horses must be interpreted in light of the exposure of racing Thoroughbreds to intensive exercise and large feedings of concentrate. None of the aforementioned management factors is uniformly either necessary or sufficient to cause colic. (That is, changing a horse's diet does not always cause colic.) However, each factor may contribute to development of colic, and modification of management factors can help reduce the incidence of the health problem.

Colic comprises a wide range of disorders, resulting in clinical signs of abdominal pain. Epidemiologic studies of specific types of colic (e.g., impaction of the large colon) may identify risk factors that are more specific for certain types of colic.

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## CHAPTER 3.6

# Gastric Outflow Obstruction in Young Horses

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**D**elayed gastric emptying is not a definitive diagnosis but describes a clinical syndrome that is a result of an underlying disorder or disorders. When encountered in foals of suckling or weanling age, delayed gastric emptying most frequently develops secondary to gastroduodenal ulceration, duodenitis, or stenosis of the pylorus and/or duodenum.

The flow of material from the stomach to the small intestine proceeds through the pylorus. The pylorus is not a true sphincter; that is, it does not control gastric emptying by reflex opening and closing. Rather, the pylorus retains feed in the gastric lumen until mixing and churning have reduced solid ingesta into tiny particles suitable for maximum surface exposure to the digestive enzymes encountered in the proximal small bowel. The pyloric sphincter prevents passage of large particles of solid food into the duodenum and also reflux of duodenal contents into the stomach but plays no important role in regulating the rate of gastric emptying of liquid contents. The true determinant of gastric emptying is the pressure gradient that develops with each cycle of gastric contraction between the stomach and the duodenum. These waves of gastric peristalsis are responsible for the passage of fluid through the pylorus.

Waves of peristalsis across the stomach are regulated by the autonomic nervous system. Stimulation of the vagus nerve increases motility, and stimulation of the sympathetic nervous supply inhibits motility. The composition of the ingesta reaching the duodenum also determines the rate of gastric emptying. Fat, fatty acids, peptides, and sugars—on reaching the duodenum—slow the rate of gastric emptying by reducing the peristaltic activity in the gastric walls. Although 10 to 12 hours or longer may be required to evacuate fully the stomach of solid feed in adult horses, the passage time for milk in young foals is about 2 hours or less. Passage times greater than 2 hours should be considered delayed.

### CLINICAL SIGNS

Severe gastroduodenal ulcer syndrome can lead to delayed emptying in the following two ways:

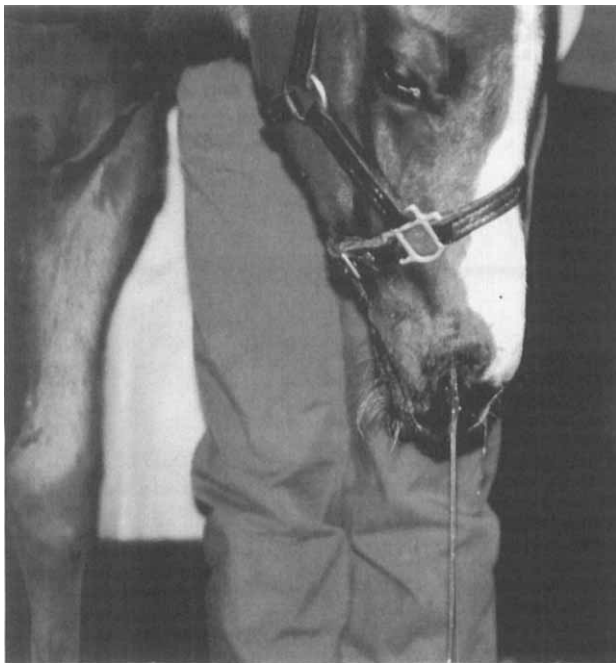
1. Through functional disruption of gastric motility patterns
2. By inflammatory pyloric obstruction

Foals with gastric outflow obstruction typically present with colic or lethargy. Foals are generally less tolerant of

abdominal pain than adults, and many foals with outflow obstruction demonstrate clear signs of abdominal discomfort. Other foals primarily demonstrate dullness and inappetence; they may paw occasionally or remain quietly recumbent and may develop more intensified signs of colic after nursing. Some foals begin to nurse and then abruptly cease and appear disgruntled or agitated, presumably because of gastric pain. Some combination of clinical signs referable to gastroduodenal ulceration—including bruxism, lying in dorsal recumbency, colic, diarrhea, and salivation—also may be apparent. Affected foals typically have an unthrifty, potbellied appearance and appear small and lethargic compared with healthy same-aged foals. Many affected foals have demonstrated past signs of gastric or duodenal ulceration, but in others, no previous clinical indications of gastric ulceration may have been evident. Foals occasionally present in such a critical state of gastric distention that gastric contents are leaking from the nostrils (Figure 3.6-1).

Endoscopically detectable gastric ulceration is present in 30% to 50% of healthy-appearing foals, and this author's opinion is that the frequency of ulcers and their complications is much greater when foals have enteric disease. Therefore the medical history is an important component of the database for affected foals. Many foals presenting with gastric outflow obstruction have recovered from a recent bout of diarrhea or nondiarrheal enteritis but fail to thrive and begin showing signs of colic, inappetence, and poor body condition in the days to weeks after apparent resolution of the problem. Such foals may no longer have diarrhea and may not show clinical signs of ulcer pain at the time of presentation. Dried stool in the tail and a hairless area on the rump from previous fecal scalding are clues of recent diarrhea.

The presentation of a foal in the 2- to 6-month age range with depression, colic, variable fever, an unthrifty appearance, and any combination of signs of gastric ulceration, which has a history of previous diarrhea or nondiarrheal enteritis, is a typical clinical presentation of a foal with gastric outflow obstruction. Many foals presenting to this author's clinic that are diagnosed with outflow obstruction have been treated with a course of antiulcer medications, including  $H_2$  antagonists or omeprazole, suggesting a failure of these drugs to prevent gastric and duodenal ulceration and their complications in some circumstances. The apparent failure of these drugs to prevent ulceration may reflect an inability of even effective therapeutic agents

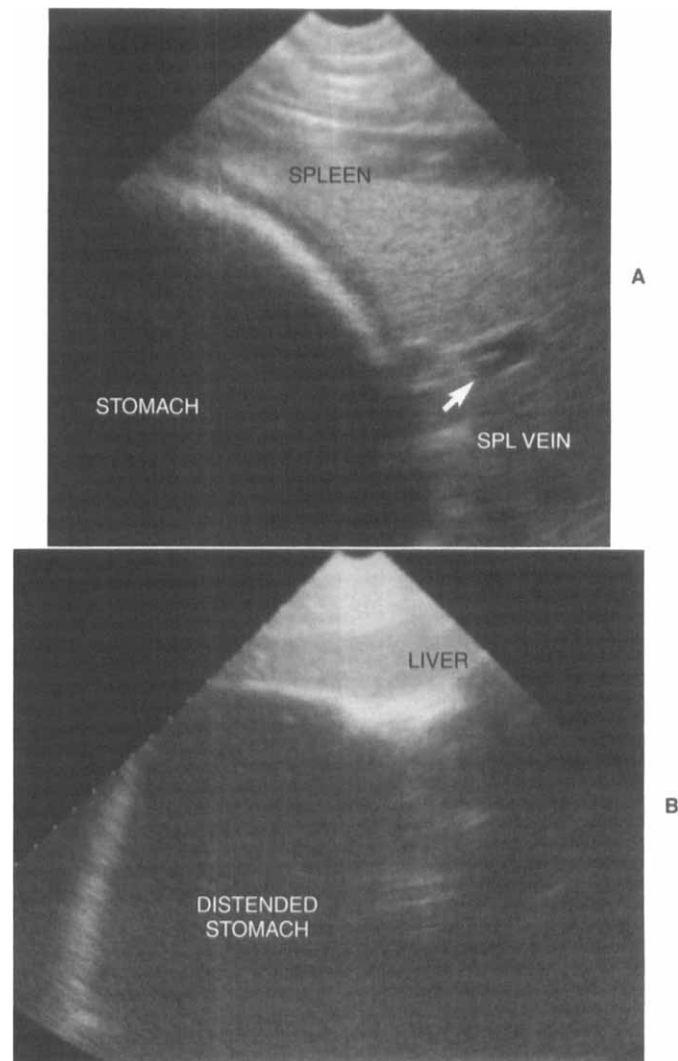


**Figure 3.6-1** Weanling with stenosis of pylorus and duodenum secondary to severe gastroduodenal ulceration. The mental depression and ptyalism are typical of foals with this syndrome.

to work in situations in which anatomic problems restrict the normal removal of acidic fluid from the stomach interior or when concurrent illness alters normal blood flow to gastric mucosa.

## DIAGNOSIS

Diagnosis of delayed gastric emptying is based on clinical signs, endoscopy, and ultrasound findings. Ultrasound imaging of foals with gastric outflow obstruction reveals gastric distention, sometimes marked, with a fluid-gas interface line near the dorsal-most aspect of the stomach (Figure 3.6-2). The stomach is imaged on the foal's left side between rib spaces 8 and 14, with a greater area—sometimes much of the left and ventral aspect of the foal's abdomen—being taken up when gastric distention is severe. The duodenum may be characterized by mural edema and increased thickness and reduced peristalsis. The lumen size may appear greatly reduced. In such cases, when viewed in the upper right paralumbar fossa cranial to the right kidney, the duodenum has a thick-walled, cigarlike appearance, with inadequate luminal capacity to permit the passage of feed. This appearance correlates with edema, inflammation, and fibrosis in the submucosal layer of the duodenum. Although the pylorus cannot be imaged with ultrasound, the appearance of severe gastric distention and duodenitis as described suggests that the pyloric tissue is affected similarly and that edema, fibrosis, and possible stricture formation have occurred and are responsible for the delayed removal of ingesta. Ultrasound findings that also may be present include signs of enteritis or colitis with dilation of intestinal segments and liquid contents. Foals with low albumin and oncotic pressure often show some degree of intramural edema and increased mural thickness throughout much of the small and large intestinal length.



**Figure 3.6-2** **A**, Ultrasound image showing a normal stomach in relation to the spleen and splenic vein, *in situ* in the left cranial abdomen. Note the tightly curved configuration of the stomach, denoting normal gastric volume and suggesting normal emptying patterns. The left side of the image is dorsal. The image was made with a 5.0-MHz sector probe with a displayed depth of 14 cm. **B**, Ultrasound image of distended stomach. The white vertical linear echo of the left side of the image denotes fluid-gas interface in the gastric interior. The left side of the image is dorsal. Notably, the stomach's normal curvilinear boundary is absent, and the normal spatial relationship with the splenic hilus is missing. Only a small wedge of liver can be appreciated in proximity to the stomach. The stomach's walls are obviously distended by gas-flecked anechoic fluid. The image was made with a 5.0-MHz sector probe with a displayed depth of 18 cm.

If sonographic imaging reveals gastric distention that does not resolve after muzzling the foal for 2 to 4 hours, in addition to the appearance of duodenal thickening, a diagnosis of outflow obstruction should be suspected.

Blood work in foals affected by delayed gastric emptying is nonspecific. Changes may reflect ongoing and active bowel inflammation, with the common attendant derangements of dehydration, leukopenia, neutropenia, hypochloremia, and acidosis. Inappetence leads to the ad-

ditional development of hypokalemia and hypocalcemia. Hypoproteinemia caused by hypoalbuminemia is frequently present in foals with this syndrome at this author's clinic and reflects either the protein-losing nature of whatever enteropathy the foal is concurrently experiencing or blood loss from ulcers. For example, foals that have recently recovered from rotaviral enteritis, *Salmonella* typhlocolitis, *Lawsonia* infection, cyathostomiasis, or non-diarrheal enteritis would be considered at an increased risk for the development of gastroduodenal ulcer syndrome. The loss of oncotic pressure from albumin loss across inflamed intestinal mucosa likely exacerbates the mural edema and thickening in the pylorus and duodenum. This scenario is very common.

In foals in which the condition has been present for some time, changes in the blood profile are more likely to reflect leukocytosis resulting from neutrophilia and hyperfibrinogenemia and changes reflective of dehydration. Anemia is frequently present and may occur as a result of bleeding from ulcers and from the physiologic depression in hematocrit that occurs with chronic disease. Electrolyte concentrations may be variable in such cases. Changes in blood profiles are nonspecific but helpful in pointing to the presence of concurrent disease and thus to an animal with a heightened likelihood of having delayed outflow when the clinical findings are supportive.

Endoscopy permits visual verification of ulceration and stenosis of the pylorus and/or duodenum. If the practitioner does not have gastroscopic capabilities, clinical signs of gastric or duodenal ulcers would strongly add to the index of suspicion, as would a history or current finding of diarrhea or enteritis. A history of the foal having been administered  $H_2$  antagonists or omeprazole should not preclude the consideration that severe gastroduodenal ulcers have developed.

## TREATMENT

Medical and surgical methods are used to treat delayed gastric emptying resulting from pyloric or duodenal stenosis. The response to either modality is often disappointing, and a guarded prognosis should be given to owners who elect to pursue treatment in the interest of salvaging the animal for eventual breeding purposes. In foals with severe gastric distention and colic, therapy begins with decompression of the stomach via nasogastric intubation and siphoning. Foals presenting to this author's clinic with obstructed outflow often are managed with indwelling nasogastric tubes to facilitate serial removal of reflux fluid. Muzzling to prevent excessive milk intake, total parenteral nutritional support, intravenous (IV) polyionic fluids with electrolyte supplementation as dictated by serial blood monitoring, IV broad-spectrum antibiotics, prokinetics, and antiulcer medications form the basis of attempts to support and medically manage affected foals. In foals that have concurrent hypoalbuminemia and hypoproteinemia, additional measures to restore oncotic pressure—such as administration of hetastarch, plasma, or equine albumin—also may be pursued. Fever should be managed as much as possible with fans, alcohol baths, and cooling of any IV fluids that are

administered. When nonsteroidal antiinflammatory drugs (NSAIDs) are deemed necessary, those agents that are less ulcerogenic, such as ketoprofen, should be used judiciously.

Gastrointestinal (GI) prokinetic agents such as metoclopramide and bethanechol may be helpful at promoting gastric emptying. Metoclopramide, a substituted benzimidazole drug, increases competency of the cardiac sphincter and decreases gastroesophageal reflux while enhancing forward gastric and small intestinal motility. The drug can be delivered via the oral, subcutaneous, or slow IV infusion routes; parenteral administration is preferred in foals with outflow obstruction. Severe central nervous system (CNS) excitatory effects sometimes attend usage of metoclopramide, and the drug's margin of safety is relatively narrow. A dosage range of 0.05 to 0.15 mg/kg every 8 hours subcutaneously or via slow IV infusion is usually effective while minimizing untoward effects.

Bethanechol is a cholinergic agonist and has been administered effectively to foals with delayed gastric emptying. The drug reportedly enhances gastric motility without promoting further acid secretion and can be given via the subcutaneous or oral routes at dosages of 0.025 to 0.030 mg/kg every 4 to 6 hours or 0.35 mg/kg every 6 to 8 hours, respectively. Currently, bethanechol must be obtained from compounding pharmacies because commercial production has been discontinued.

If medical therapy is not promptly successful at restoring forward GI motility, surgical intervention should be considered. The goal of surgical treatment for obstructed gastric outflow is to bypass the affected sections of pylorus and duodenum. The gastrojejunostomy technique typically is used and may be helpful in some cases, although the response to this intervention is frequently disappointing. Some surgeons recommend a second surgery to reverse the procedure after several months. Surgery is only modestly successful at reversing the chronic colic, poor growth, catabolic state, and need for protracted medical treatment. As is true with the choice to proceed to surgery for other causes of colic, the decision for surgical management in these foals should not be delayed and chosen only as a last resort, after a significant decline in patient status. Because fasting and keeping the stomach decompressed and empty through serial refluxing exacerbate luminal acidity, failure of medical therapy to elicit a prompt positive response should be an indication to proceed to surgical intervention sooner, rather than later, in the clinical course of the disease. The catabolic state and severe damage to the proximal portion of the GI tract in affected foals probably factors importantly into the poor postoperative performance and long-term survival rate.

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## CHAPTER 3.7

# Endotoxemia

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When gram-negative bacteria multiply or lyse on bacterial cell death, a structural lipopolysaccharide component is released from their outer cell membrane. This heat-stable lipopolysaccharide (LPS), commonly referred to as *endotoxin*, has three structural components: (1) a highly variable outer polysaccharide “O-antigenic” region, (2) a core region consisting mostly of monosaccharides, and (3) the highly conserved toxic moiety, lipid A.

The enormous resident population of gram-negative bacteria in the equine intestinal tract produces a tremendous reservoir of endotoxin. This source of endotoxin normally is confined to the lumen of the healthy intestine by protective mucosal barriers. However, if the intestinal wall is damaged by ischemia, infection, inflammation, hypoxemia (e.g., hemorrhagic shock or strenuous exercise), or trauma, the otherwise contained endotoxin gains access to the circulation. With the high incidence of acute gastrointestinal (GI) disease in adult horses, endotoxemia is a common sequela to colic. At referral institutions, as many as 30% of horses examined for acute colic have detectable levels of endotoxin in their blood at the time of admission.

Although endotoxemia often is associated with acute GI disease, the release of endotoxin during log-phase bacterial growth puts any horse with gram-negative sepsis at risk of becoming endotoxemic. As many as 50% of foals with gram-negative septicemia are endotoxemic at the time of their initial examinations. Septicemia is uncommon in adult horses; however, intense localized gram-negative sepsis, such as occurs with pleuropneumonia, peritonitis, *Salmonella* colitis, or metritis is frequently accompanied by endotoxemia. Whether released from endogenous sources, such as the intestinal lumen of a horse with colic, or from overwhelming gram-negative sepsis, the net effects of endotoxin are similar. Small amounts of endotoxin that escape into the interstitium, lymphatics, and eventually the bloodstream are effectively phagocytized by Kupffer cells in the liver or are neutralized by LPS binding substances in the blood, such as natural anti-LPS antibodies and high density lipoproteins. Only when excessive amounts of endotoxin gain access to the circulation does the situation become problematic.

### PATHOPHYSIOLOGY

Once in the blood, endotoxin’s amphipathic properties cause it to form aggregates that otherwise spontaneously

disperse into monomers at a very slow rate. LPS binding protein, a plasma constituent, efficiently extracts molecules of endotoxin from aggregated micelles in the blood and serves as a transporter, rapidly delivering endotoxin to the surface of cells bearing cluster differentiation antigen 14 (CD14), most notably, monocytes and neutrophils. CD14 is a well-conserved bacterial pattern-recognition receptor that is attached to the outer cell membrane by a glycosylphosphatidylinositol anchor. Because CD14 does not have a transmembrane domain, it must associate with Toll-like receptor 4 and its cofactor, MD2, to activate intracellular signaling pathways that ultimately result in the synthesis and release of a myriad of proinflammatory mediators. In addition to membrane-bound CD14, unbound soluble isoforms of CD14 are found in the plasma of healthy animals and may confer endotoxin responsiveness to cells that do not bear CD14. Recently, CD14 also has been shown to bind gram-positive bacterial components, such as lipoteichoic acid and peptidoglycan, which induce cell activation in a fashion similar to endotoxin.

Although experts debate about which intracellular signaling systems are most important in endotoxin-induced cell activation, they agree that most of the deleterious effects of endotoxin are the result of endogenously synthesized mediators. The most widely studied of these mediators are the metabolites of arachidonic acid (the prostaglandins, thromboxane, and the leukotrienes), platelet activating factor, cytokines (tumor necrosis factor and interleukins 1 and 6), vasoactive and chemotactic peptides (histamine, serotonin, bradykinin, complement components), tissue factor, proteolytic enzymes, and reactive oxygen species. Cells bearing CD14 assuredly play a substantial role in initiating the response to endotoxin. However, endotoxin has some direct effects, such as the activation of coagulation factor XII and interaction with cells through CD14 independent pathways.

The culmination of events in endotoxemia involves overzealous inflammation, immunosuppression, alterations in hemodynamics, and coagulopathy. Moderate doses of endotoxin cause early systemic hypertension (“hyperdynamic phase”), followed soon after by a sustained drop in blood pressure (“hypodynamic phase”). Decreased peripheral vascular resistance, myocardial depression, hypovolemia, and microvascular thrombosis all contribute to reduction of blood flow to vital organs that may become so intense that the process is irreversible.

## CLINICAL SIGNS AND DIAGNOSIS

In many situations the clinical signs of the disease process responsible for endotoxemia are obvious and actually may overshadow recognition of endotoxemia. When intestinal ischemia or inflammation is responsible for transmural movement of endotoxin, signs of colic often predominate and should alert the clinician to further investigate the abdominal cavity. Transrectal palpation in the adult horse, abdominocentesis, and transabdominal ultrasonography may be helpful in identifying ischemic or inflammatory conditions of the GI tract or peritonitis. Often horses with impending colitis present only with signs of endotoxemia, posing a diagnostic challenge in the absence of signs of abdominal pain or diarrhea. In such animals, colitis can be suspected only after elimination of other potential causes for endotoxemia.

If signs of endotoxemia are present in the absence of signs of abdominal pain, then the likely supposition for the source of endotoxin is gram-negative infection. Unlike in adult horses, gram-negative septicemia is the most likely reason for endotoxemia in neonates. In adult horses, pneumonia, especially pleuropneumonia, septic peritonitis, *Salmonella* colitis, and postpartum metritis are the most likely sources of gram-negative infection. A thorough examination of the thoracic cavity (auscultation with a rebreathing bag, radiography, ultrasonography, or transtracheal aspiration), abdominocentesis, and transrectal palpation or ultrasonography of the uterus in postpartum mares may be helpful in identifying the source of endotoxin.

Most of the clinical signs and physical examination findings of endotoxemia are not specific. When endotoxin is given intravenously (IV) to horses, it induces fever, mild to moderate abdominal pain, depression, yawning, anorexia, hyperemic mucous membranes, prolonged capillary refill time, decreased GI sounds, tachycardia, tachypnea, sweating, cow-pie-consistency feces, and dehydration. Perhaps one of the most reliable clinical signs of endotoxemia is the presence of a "toxic line," a bright pink to bluish-purple line of discoloration at the periphery of the gingiva around the incisors. With prolonged or severe endotoxemia, signs of cardiovascular collapse and multiple organ failure predominate. Typically these horses are stuporous; have cold extremities, profuse sweating, weak peripheral pulses, muscular tremors, diffusely purple and congested mucous membranes, prolonged jugular refill time, dependent pitting edema, laminitis, oliguria or anuria, and abdominal distention from ileus; and may have signs of disseminated intravascular coagulopathy (petechial or ecchymotic hemorrhages, spontaneous jugular thrombosis, frank hemorrhage). These later signs generally are associated with a poor to grave prognosis.

Leukopenia, characterized by neutropenia; increased numbers of band neutrophils; and the presence of toxic morphology in neutrophils (Döhle bodies, basophilic cytoplasm, vacuolization, or granulation) are classic hematologic changes seen during acute endotoxemia or overwhelming bacterial infection. Other clinicopathologic changes that accompany endotoxemia are nonspecific but may include hemoconcentration, azotemia, metabolic acidosis, hyperglycemia in adults, hypoglycemia in neonates, increased anion gap, hypocalcemia, increases in cellular

enzymes (lactic dehydrogenase, aspartate aminotransferase, sorbitol dehydrogenase,  $\gamma$ -glutamyl transferase, and creatine kinase), and hypoxemia. Total serum protein may be normal, increased from dehydration, or decreased, if protein-losing enteropathy, pleuritis or peritonitis is present. Thrombocytopenia, prolongation of the activated partial thromboplastin time and prothrombin time, and increased concentration of fibrin degradation products are hallmark signs of disseminated intravascular coagulopathy. Electrolyte loss is most frequent when endotoxemia is caused by enterocolitis.

The presence of clinical signs of endotoxemia—especially the occurrence of a "toxic line," in combination with neutropenia and toxic neutrophil morphology—is sufficient evidence of endotoxemia. Definitive diagnosis of endotoxemia can be achieved through quantification of endotoxin in the plasma with the Limulus ameobocyte lysate assay. The assay is based on the principle that the ameobocyte, a blood cell from the horseshoe crab (*Limulus polyphemus*) produces substances that initiate coagulation on contact with endotoxin. Plasma endotoxin concentrations in naturally occurring cases in foals and horses have been reported in the picogram to nanogram per milliliter range. The assay is somewhat tedious and inconvenient for routine detection of endotoxemia in clinical cases.

## CLINICAL MANAGEMENT

The rapid response to endotoxin coupled with the diverse biologic actions of the endogenous mediators present a difficult therapeutic challenge. Although neutralization of endotoxin or blockade of a single class of mediators may provide some benefit, no single treatment is a panacea. Rather, treatment of endotoxemia should include a combination of therapeutic agents. Considering the potential sources of endotoxin and the current knowledge concerning the cellular response to endotoxin, the following five primary therapeutic targets should be considered:

1. Prevention of the release of endotoxin into the circulation
2. Neutralization of endotoxin before it interacts with inflammatory cells
3. Prevention of endotoxin-induced cellular activation
4. Prevention of the synthesis, release, or action of specific endogenous mediators
5. General supportive care

### Prevention of the Release of Endotoxin into the Circulation

The first important step in treating endotoxemia is identification of its source. If ischemic bowel is suspected, an exploratory celiotomy is warranted. Surgical resection of damaged intestine alleviates signs of colic and prevents further leakage of endotoxin. If nonsurgical inflammatory lesions of bowel, such as proximal enteritis or colitis, are responsible for endotoxemia, little can be done immediately to directly halt transmural movement of endotoxin. In these scenarios, attention is directed toward antiinflammatory therapy and neutralization of endotoxin or its mediators.



To cease proliferation of bacteria and thus diminish further release of endotoxin, antimicrobial therapy is essential in the treatment of neonatal septicemia or localized gram-negative infection and should ultimately be guided by patient-specific antimicrobial sensitivity data. However, bactericidal therapy, particularly with drugs that inhibit cell wall biosynthesis, may result in the release of endotoxin. Abundant experimental data from *in vitro* and *in vivo* animal models, including foals, have demonstrated that  $\beta$ -lactam antibiotics and the quinolones cause the release of large quantities of endotoxin during bactericidal therapy against gram-negative bacteria, compared with aminoglycosides. Furthermore,  $\beta$ -lactam-induced release of endotoxin is accompanied by a more rigorous inflammatory response. With this information in mind, use of inhibitors of cell wall biosynthesis should be accompanied by drugs that bind and neutralize endotoxin. Drainage of septic fluid or lavage at sites of infection may also be useful to decrease the bacterial load in cases of pleuritis, peritonitis, or metritis.

### Neutralization of Endotoxin before It Interacts with Inflammatory Cells

Once endotoxin enters the circulation, an ideal therapeutic strategy would be to bind and neutralize endotoxin before it interacts with CD14 on host inflammatory cells. Currently in horses, two such products that directly bind to endotoxin are commercially available: antiendotoxin antibodies and polymyxin B. Antiendotoxin antibodies are harvested from horses vaccinated with the exposed core regions of rough strains of J5 *Escherichia coli* or *Salmonella* Typhimurium, which hypothetically should cross-react with the highly conserved core region of endotoxins from most gram-negative bacteria. Anticore antibodies have been used in several clinical and experimental trials, often with conflicting results. In some studies, treatment with antiendotoxin antibodies resulted in reduced mortality and fewer days of hospitalization, compared with placebo-treated horses. In contrast, the effects of such products in other studies have been equivocal. Several potential reasons exist for these discrepancies, one of which is the timing of treatment. Because of endotoxin's rapid interaction with cells and the fact that antiendotoxin antibodies can not "turn off" the effects of cellular-bound endotoxin, early treatment with antibodies provides more therapeutic benefit than treatment late in the course of endotoxemia. The anticore antibodies may be unable to penetrate micelles of endotoxin or intact O-side chains of smooth native endotoxin.

Endoserum (Immvac, Inc, Columbia, Mo.), hyperimmune serum from horses vaccinated with the *S. Typhimurium* Re mutant, requires refrigeration and is costly. The recommended label dose for treatment of endotoxemia is 1.5 ml/kg body weight intravenously. Dilution of this product with sterile isotonic saline or lactated Ringer's solution (1:10 to 1:20) and administration of the diluted product intravenously over 1 to 2 hours may reduce the risk of immune-mediated hypersensitivity reactions. Experimental and anecdotal reports state that Endoserum is more likely to have adverse effects in endotoxemic foals. With this information in mind, hyperimmune anticore

plasma may be more appropriate for use in neonates. It can be used in foals for the concurrent treatment of endotoxemia, septicemia, and failure of passive transfer, given at the dose recommended for treatment of failure of passive transfer (20-40 ml/kg body weight). The plasma products have the disadvantage of requiring freezer storage. *E. coli* J5 and *S. Typhimurium* hyperimmune plasma are available from two commercial sources in the United States (Veterinary Dynamics, Inc., San Luis Obispo, Calif., and Lake Immunogenics, Inc., Ontario, N.Y.). Neither product is licensed by the U.S. Department of Agriculture; however, the companies can be contacted for specific requests for plasma lots from donors hyperimmunized with endotoxin-core antigens.

An alternative to passive immunization with the previously named products is active immunization of horses with vaccines against the core region of mutant gram-negative bacteria. This approach has provided some, but not complete, protection against subsequent challenge with endotoxin. A vaccine for use in horses is commercially available (Immvac, Inc.); however, questions remain concerning the degree and duration of protection.

Polymyxin B is a cationic polypeptide antibiotic effective against many gram-negative organisms. In addition to its bactericidal properties, it also binds to and neutralizes endotoxin through direct molecular interactions with the lipid A region. Because lipid A is conserved structurally among gram-negative bacteria, polymyxin B has broader endotoxin-binding capabilities than anticore-endotoxin antibodies. Polymyxin B has the additional advantage of being a lyophilized product that may be stored at room temperature. In addition, it is about one-fifth the cost of anticore antibodies. An impressive number of experimental and clinical studies on endotoxemia have demonstrated the effectiveness of polymyxin B, even when given hours after the onset of endotoxemia.

The endotoxin-binding properties of polymyxin B have been known for decades, but its clinical use has been hindered by its inherent adverse nephrotoxic and neurotoxic side effects when used intravenously at bactericidal doses. Recent studies in both human patients and horses have shown that doses considered suboptimal for bactericidal treatment are remarkably effective in neutralizing endotoxin without causing toxic side effects. Currently in horses the recommended dose of polymyxin B is 1000 to 6000 IU/kg body weight intravenously every 8 to 12 hours. In most clinical situations the release of endotoxin is diminished as the underlying disease process resolves or endotoxin tolerance develops; thus it is doubtful that use of polymyxin B beyond 2 to 3 days after the initial insult is beneficial. In humans, higher doses of the drug may cause neuromuscular blockade and transient apnea, and thus it is recommended on the human drug insert to dilute the product and administer it intravenously over 30 to 60 minutes. Because smaller doses are used for the treatment of endotoxemia and to this author's knowledge, apnea has not been reported at these lower doses in horses, the drug may be diluted in a small volume (20-40 ml) of isotonic saline and given intravenously over 2 to 4 minutes. Although nephrotoxicity has not been reported in experimental trials of polymyxin B at doses less than 6000 IU/kg body weight, these studies were performed in oth-



erwise healthy foals or horses challenged with endotoxin. With this information in mind, polymyxin B should be used judiciously in patients with azotemia.

### Prevention of Endotoxin-Induced Cellular Activation

A new area of exploration is the recent identification of novel LPSs isolated from purple phototrophic and nitrogen-fixing plant bacteria, such as *Rhodobacter sphaeroides* and *Rhizobium* species. The lipid A moieties from these bacteria are structurally similar to endotoxin derived from gram-negative enterics. These unique lipid A molecules bind to human monocytes, yet they do not induce activation and thus serve as effective antagonists to enteric endotoxins. However, when tested in horses, *R. sphaeroides* lipid A acted as an agonist and did not block enteric endotoxin's effects. As more is learned about what is structurally required of LPSs to bind to LPS binding protein, CD14, or Toll-like receptor 4 in horses, structurally unique or synthetic endotoxin analogs may be the treatment of the future.

### Prevention of the Synthesis, Release, or Action of Specific Endogenous Mediators

Nonsteroidal antiinflammatory drugs (NSAIDs) were one of the first classes of drugs described for the treatment of endotoxemia in horses. When compared with phenylbutazone or dipyrone, flunixin meglumine (1.1 mg/kg IV) was the NSAID most effective in preventing endotoxin-induced prostanoid synthesis and associated clinical signs of endotoxemia. Administration of lower doses of flunixin meglumine (0.25 mg/kg IV) was more effective in preventing prostanoid synthesis than phenylbutazone at 2 mg/kg. Advantages of this "low-dose" flunixin meglumine regimen are reduced risk of potential toxic side effects, such as GI ulceration, ileus, and renal papillary necrosis and effective inhibition of prostanoid synthesis without complete masking of physical manifestations of endotoxemia that are necessary for accurate clinical assessment of the patient's progress. Ketoprofen (0.5 mg/kg IV), a proclaimed "dual inhibitor" of arachidonic acid metabolism, was as effective as "low-dose" flunixin meglumine in suppressing the effects of experimentally induced endotoxemia in horses. Its use is associated with few toxic side effects. Thus far, blockade of leukotriene synthesis by ketoprofen has not been demonstrated in horses. Another nonselective NSAID, eltenac (0.5 mg/kg IV), improved blood pressure, reduced fever and respiratory rate, and decreased prostanoid and cortisol concentrations in horses experimentally challenged with endotoxin. Recent discovery of different isoforms of cyclooxygenase (COX) has led to the introduction of selective COX inhibitors. COX-2 inhibitors could potentially provide distinct advantages over nonselective inhibitors; however, COX-2 inhibitors have not been fully evaluated in endotoxemic horses.

Although corticosteroids have been shown to inhibit release of arachidonic acid and prevent synthesis of cytokines in *in vitro* models of endotoxemia in horses, their clinical use is hampered by the suggestion that they, especially dexamethasone or triamcinolone, may potentiate the onset of laminitis in adult horses. However, a single

dose of a short-acting glucocorticoid, such as prednisolone sodium succinate (1 mg/kg IV) may offer advantages during acute endotoxemia without unduly increasing the risk of laminitis.

Inhibition of the remaining mediators associated with endotoxemia is more difficult. Although monoclonal antibodies to tumor necrosis factor and platelet-activating factor receptor antagonists have shown advantages in experimentally induced endotoxemia in horses, they are prohibitively expensive to use in horses or are not commercially available. A general lack of conclusive evidence exists that blockade of lipid peroxidation by use of superoxide dismutase, allopurinol, or dimethyl sulfoxide (DMSO) is beneficial in experimentally induced endotoxemia in horses. Nonetheless, DMSO frequently is used IV at doses ranging from 0.1 to 1 g/kg, diluted to at least 10% in fluids. Higher doses of DMSO may exacerbate reperfusion injury of the equine intestine, and thus if endotoxemia is caused by intestinal ischemia, lower doses of DMSO should be considered. A recommended IV dose of allopurinol in endotoxemic horses is 5 mg/kg.

Pentoxifylline is a phosphodiesterase inhibitor currently available for use in humans as a rheologic agent, increasing regional blood flow. In addition to its rheologic effects in horses, pentoxifylline has been shown to block endotoxin-induced cytokine, thromboxane, and thromboplastin production. This combination of effects may be particularly useful in horses at high risk for developing laminitis in association with endotoxemia. It is safely given to horses orally at a dose of 8 mg/kg every 8 hours. It is not available commercially in an IV preparation.

### General Supportive Care

A key element in the treatment of endotoxic or septic shock is restoration of normovolemia, which can be achieved by IV administration of isotonic polyionic fluids (20-40 ml/kg/hr), the type and rate of fluid administration being dictated by the primary disease responsible for endotoxemia (see Chapter 3.10: "Management of Pain and Dehydration in Horses with Colic"). Particular attention should be paid to the total volume and rate of IV fluid administration because endothelial damage in endotoxemic patients may promote edema formation, especially if fluid administration is overzealous. If large volumes of isotonic fluids are not available, smaller volumes (4 ml/kg IV) of hypertonic (7.5%) saline solution have been shown to restore normovolemia and cardiovascular status in endotoxemic horses. Hypertonic saline must be used with caution in horses with underlying sodium derangements. Total body fluid deficits ultimately must be replaced by isotonic fluids. Vasoactive compounds, such as dopamine or dobutamine, also can be used to increase tissue perfusion. The results of studies performed in anesthetized horses suggest that administration of dopamine at a dose rate of 2.5  $\mu$ g/kg/min increases cardiac output and blood pressure during endotoxemia. Continuous IV infusion of lidocaine has been shown to improve cardiovascular status and decrease mediator synthesis in endotoxemic rabbits. Although lidocaine has not been fully evaluated in endotoxic shock in horses, it is frequently used for the treatment of postoperative ileus (3 mg/kg/hr).

Horses with prolonged or severe endotoxemia are at greater risk for developing vascular thrombosis, disseminated intravascular coagulopathy (DIC), laminitis, renal failure, septic thrombophlebitis at indwelling catheter sites, respiratory disease, ileus, abortion, and myocarditis and therefore should be closely monitored for these sequelae. Endotoxin-induced coagulopathy, most notably DIC, is best treated by removal of the underlying cause and administration of fresh heparinized plasma. Unfractionated heparin therapy has been shown to reduce the severity of laminitis in a carbohydrate-overload model in ponies and in naturally occurring proximal enteritis and thus may be beneficial in endotoxemia caused by grain engorgement or enteritis. Use of unfractionated heparin for endotoxemia has been hindered by the fact that when administered subcutaneously or intravenously to horses, it markedly increases red blood cell agglutination *in vitro*. If this same phenomenon occurs *in vivo*, unfractionated heparin could exacerbate microvascular plugging associated with endotoxemia. The antithrombotic effect of low-molecular-weight heparin is comparable to unfractionated heparin, and the former does not cause erythrocyte agglutination in horses. A recommended subcutaneous dosage for low-molecular-weight heparin in horses is 50 IU/kg every 24 hours. Aspirin therapy may deter the development of thrombi and can be safely given orally at 10 mg/kg body weight every 48 hours. Pregnant mares that become endotoxemic are at risk of aborting their fetuses. Administration of altrenogest orally (44 mg) or flunixin meglumine (1.1 mg/kg IV) is effective in preventing abortion in endotoxemic mares, especially during the first 60 days of pregnancy.

If gram-negative sepsis or septicemia initiates endotoxemia, antimicrobial therapy is a necessity. When using antibiotics for the treatment of gram-negative sepsis, the clinician may use adjunct treatment with endotoxin-binding agents, such as polymyxin B. In adult horses, endotoxemia

more commonly is associated with enteric disease, rather than septicemia, and thus use of antimicrobials is controversial. Antimicrobial therapy may alter the distribution of normal gut flora, thereby exacerbating GI disease. Nonetheless, endotoxemia can cause profound neutropenia and general immunosuppression that may predispose affected horses to localized sepsis (e.g., at IV catheter sites) or septicemia. Thus the potential prophylactic benefit of antimicrobial therapy in adult horses with enteric disease that is accompanied by severe or prolonged neutropenia or preexisting localized infection at any location may outweigh its potential adverse effects on gut flora.

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## CHAPTER 3.8

# Modulation of Intestinal Motility and Ileus

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**I**leus, the functional impairment of aboral transit of intestinal contents, is seen as a consequence of intestinal ischemia and distention, peritonitis, electrolyte imbalances, endotoxemia, anesthesia, and surgical trauma to the intestine. In horses, ileus is associated primarily with disorders of the small intestine. The most common type of disorders in which ileus is detected are surgical lesions of

the small intestine, such as strangulating lipomas, segmental volvulus, and various internal and external hernias. Postoperative ileus (POI) is one of the most commonly encountered complications in horses after surgical colic, accounting for 21% to 85% of postoperative complications. Although management of horses that develop ileus has markedly improved, with reported mortality

Horses with prolonged or severe endotoxemia are at greater risk for developing vascular thrombosis, disseminated intravascular coagulopathy (DIC), laminitis, renal failure, septic thrombophlebitis at indwelling catheter sites, respiratory disease, ileus, abortion, and myocarditis and therefore should be closely monitored for these sequelae. Endotoxin-induced coagulopathy, most notably DIC, is best treated by removal of the underlying cause and administration of fresh heparinized plasma. Unfractionated heparin therapy has been shown to reduce the severity of laminitis in a carbohydrate-overload model in ponies and in naturally occurring proximal enteritis and thus may be beneficial in endotoxemia caused by grain engorgement or enteritis. Use of unfractionated heparin for endotoxemia has been hindered by the fact that when administered subcutaneously or intravenously to horses, it markedly increases red blood cell agglutination *in vitro*. If this same phenomenon occurs *in vivo*, unfractionated heparin could exacerbate microvascular plugging associated with endotoxemia. The antithrombotic effect of low-molecular-weight heparin is comparable to unfractionated heparin, and the former does not cause erythrocyte agglutination in horses. A recommended subcutaneous dosage for low-molecular-weight heparin in horses is 50 IU/kg every 24 hours. Aspirin therapy may deter the development of thrombi and can be safely given orally at 10 mg/kg body weight every 48 hours. Pregnant mares that become endotoxemic are at risk of aborting their fetuses. Administration of altrenogest orally (44 mg) or flunixin meglumine (1.1 mg/kg IV) is effective in preventing abortion in endotoxemic mares, especially during the first 60 days of pregnancy.

If gram-negative sepsis or septicemia initiates endotoxemia, antimicrobial therapy is a necessity. When using antibiotics for the treatment of gram-negative sepsis, the clinician may use adjunct treatment with endotoxin-binding agents, such as polymyxin B. In adult horses, endotoxemia

more commonly is associated with enteric disease, rather than septicemia, and thus use of antimicrobials is controversial. Antimicrobial therapy may alter the distribution of normal gut flora, thereby exacerbating GI disease. Nonetheless, endotoxemia can cause profound neutropenia and general immunosuppression that may predispose affected horses to localized sepsis (e.g., at IV catheter sites) or septicemia. Thus the potential prophylactic benefit of antimicrobial therapy in adult horses with enteric disease that is accompanied by severe or prolonged neutropenia or preexisting localized infection at any location may outweigh its potential adverse effects on gut flora.

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## CHAPTER 3.8

# Modulation of Intestinal Motility and Ileus

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**I**leus, the functional impairment of aboral transit of intestinal contents, is seen as a consequence of intestinal ischemia and distention, peritonitis, electrolyte imbalances, endotoxemia, anesthesia, and surgical trauma to the intestine. In horses, ileus is associated primarily with disorders of the small intestine. The most common type of disorders in which ileus is detected are surgical lesions of

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rates dropping from 86% to 13% in horses that develop ileus, POI is still associated with 40% of all postoperative deaths in horses treated for colic. Ileus accompanied by large volumes of nasogastric reflux is also the hallmark clinical abnormality in horses with anterior enteritis. Other conditions associated with ileus are impaction colic and some cases of severe colitis.

## PHYSIOLOGY AND PATHOPHYSIOLOGY OF GASTROINTESTINAL MOTILITY

Multiple factors influence gastrointestinal (GI) motility. In general, the sympathetic nervous system provides inhibitory input while the parasympathetic nervous system provides excitatory input. The parasympathetic system is composed of preganglionic fibers, which synapse with postganglionic fibers, the cell bodies of which are contained within the enteric ganglia. The parasympathetic fiber releases acetylcholine, which stimulates nicotinic receptors to excite postganglionic fibers. The postganglionic fibers are either cholinergic excitatory fibers acting on muscarinic receptors on enteric smooth muscle or non-adrenergic-noncholinergic inhibitory fibers. In the sympathetic system, preganglionic fibers synapse with postganglionic fibers, the cell bodies of which are within prevertebral ganglia. The postganglionic sympathetic fibers terminate on presynaptic excitatory cholinergic neurons and inhibit the release of acetylcholine from these cholinergic nerves via release of norepinephrine. Besides this modulation from the extrinsic nervous system, clinicians should remember that the enteric nervous system has a critical role in controlling GI motility. In fact, normal motility patterns can exist without any input from the extrinsic nervous system. The enteric nervous system utilizes vasoactive intestinal peptide (VIP), nitric oxide (NO), and neuropeptides such as substance P (SP) as neurotransmitters. Abnormalities of the enteric nervous system, in addition to local events occurring in the intestinal wall such as inflammation with the release of inflammatory mediators, likely are critical factors in the development of motility disorders.

## CLINICAL SIGNS AND DIAGNOSIS

Clinical signs associated with ileus are progressive and directly related to the accumulation of gas and fluid within the GI tract as a result of the disruption of propulsive motility. If the small intestine is the primary site of pathologic processes, gastric distention usually occurs within 12 to 36 hours as fluid and gas back up from the small intestine. With increasing GI distention the horse becomes more depressed and may begin showing signs of abdominal pain. Small intestinal distention is often found on rectal palpation. If the large colon or cecum is involved, gas and fluid distention are palpable per rectum, and abdominal distention may be seen grossly. Borborygmi are usually decreased or absent. The rapid sequestration of fluid within the GI tract results in cardiovascular deterioration. The heart rate is usually elevated, the mucous membranes discolored, and the capillary refill time prolonged. Hemocentration is also reflected by an increase in the packed cell volume (PCV) and total protein. Decreases in plasma chloride, sodium, potassium, and calcium are the most

commonly observed electrolyte abnormalities. The diagnosis is based on history, clinical signs, rectal palpation, and nasogastric decompression.

## TREATMENT

Treatment should first address any predisposing causes such as electrolyte abnormalities, inflammation, pain, infection, and endotoxemia. Rarely does any form of treatment result in the immediate relief of ileus. Maintenance of the animal until the ileus resolves is critical. Nasogastric decompression to prevent rupture and to relieve proximal GI distention is the most important part of therapy. To replace the fluid lost with nasogastric decompression and to provide maintenance needs, appropriate fluid therapy is also imperative. Nonsteroidal antiinflammatory drugs (NSAIDs) to relieve pain, decrease GI inflammation, and decrease the effects of endotoxin also are recommended. Analgesics such as xylazine, detomidine, and butorphanol can all have a depressive effect on motility. However, pain also can decrease motility. Consequently, analgesics should be used when needed to reduce pain, but they should be used judiciously.

## PROKINETIC DRUGS

In most cases, the previously outlined treatment plan is effective. However, prokinetics also are administered commonly in an attempt to decrease the severity and duration of ileus. Sound clinical judgment must be used in the decision involving whether to treat a GI motility problem with a prokinetic agent. For example, cecal and large colon impactions have ruptured in response to these agents. Administering a prokinetic when the intestine is about to rupture is not likely to help the animal much and may hasten the horse's demise.

### Bethanechol

Bethanechol hydrochloride is a muscarinic cholinergic agonist that stimulates acetylcholine receptors on GI smooth muscles, causing them to contract. The rationale for using bethanechol is that parasympathetic hypoactivity is one predisposing factor for the development of ileus in horses. Bethanechol (0.025 mg/kg IV) has been demonstrated to increase the rate of gastric and cecal emptying in normal ponies. In a POI model, bethanechol (2.5 mg subcutaneously [SQ] at 2 and 5 hours postoperatively in ponies) when combined with the  $\alpha$ -adrenergic antagonist yohimbine shortened the GI transit time as measured by the passage of beads and reduced the time until normal activity levels returned throughout the GI tract. However, this drug combination was not as effective as metoclopramide in restoring gastroduodenal coordination, which was thought to be the most important indication of return to normal propulsive motility. Side effects of bethanechol arise from enhanced parasympathetic tone, including abdominal cramps, diarrhea, salivation, and gastric secretion. Side effects are thought to be reduced when the drug is administered at 0.025 mg/kg subcutaneously or orally (q3-4h). In this author's opinion, bethanechol may have a place in the treatment of gastric

and cecal impactions. However, information on this drug stems from research studies in normal horses, making it difficult to extrapolate to the pathologic state.

### Neostigmine

Neostigmine methylsulfate is a cholinesterase inhibitor that prolongs the activity of acetylcholine by retarding its breakdown at the synaptic junction. Initial work in normal horses suggested that neostigmine (0.022 mg/kg IV) stimulated propulsive motility in the pelvic flexure but delayed gastric emptying and decreased propulsive motility in the jejunum. However, other data showed that neostigmine at a similar dose increased the amplitude of rhythmic contractions in both resting and distended small intestines in anesthetized horses. This last finding suggests that neostigmine may be beneficial in treating ileus associated with small intestinal motility disorders. The dose recommended is 0.0044 mg/kg (2 mg per adult horse) subcutaneously or intravenously with the dose repeated every 30 to 60 minutes. If the horse does not respond and is not exhibiting any side effects, the amount can be increased in 2-mg increments to a total of 10 mg per treatment. The most common side effect is abdominal pain from intestinal spasm. The most common indication for its use seems to be large colon motility disorders associated with colitis both in foals and adults with obvious gas and fluid accumulation in the large colon. Some surgeons like to use neostigmine to empty the colon after correcting a large colon displacement or volvulus. This author prefers to empty the colon at surgery through a pelvic flexure enterotomy because retrospective data have shown that evacuation of ingesta through a pelvic flexure enterotomy decreases the incidence of POI. Other potential indications for neostigmine are cecal impactions, nonresponsive large colon impactions, sand impactions, and small colon impactions.

### Acepromazine and Yohimbine

Both acepromazine and yohimbine are  $\alpha$ -adrenergic antagonists. Their use in treating ileus is based on the assumption that sympathetic hyperactivity contributes to motility disturbances. Acepromazine maleate facilitates small intestinal transit in normal ponies. Based on clinical impressions, acepromazine administered at 0.01 mg/kg intramuscularly every 4 hours is thought to reduce the severity of POI in horses with small intestinal lesions. Because acepromazine is a nonselective  $\alpha$ -adrenergic blocker and causes peripheral vasodilation, the animal should be well-hydrated before the drug is administered. Yohimbine hydrochloride (Yobine) is a selective  $\alpha_2$ -adrenergic antagonist. Consequently, it does not cause the peripheral vasodilation noted with acepromazine.  $\alpha_2$ -Adrenergic antagonists such as yohimbine counteract the increased sympathetic stimulation detected in response to nociceptive stimulation and endotoxemia. Yohimbine (0.75  $\mu$ g/kg) has attenuated the inhibitory effects of endotoxin on cecal motility. When administered at 0.15 mg/kg IV at 1, 4, 7, and 10 hours after surgery in a model of POI, yohimbine reduced the severity of POI when combined with bethanechol. It is this author's impression

that although some experimental support exists for the use of these agents in the treatment of motility disorders, they are used infrequently.

### Metoclopramide

Metoclopramide (Reglan) is a substituted benzamide with the following mechanisms of action:

1. Functions as a dopamine receptor antagonist
2. Augments the release of acetylcholine from intrinsic cholinergic neurons.
3. Has adrenergic blocking activity

All three mechanisms of action are potentially beneficial in promoting propulsive motility. Probably more data exists to support the use of metoclopramide to treat POI in horses than any other prokinetic used. In a postoperative ileus model, metoclopramide was more effective in restoring GI coordination than adrenergic antagonists and cholinomimetics administered individually or used in combination. It commonly has been administered at a dosage of 0.25 mg/kg, diluted in 500 ml of saline, administered over 30 to 60 minutes. In one study, metoclopramide administered as a continuous infusion (0.04 mg/kg/hr) decreased total volume, duration, and rate of gastric reflux when administered prophylactically after small intestinal resection and anastomosis.

In spite of this support, metoclopramide does not appear to be used very frequently. This may be due to the fact that the drug stimulates extrapyramidal side effects such as excitement, restlessness, colic, and sweating. Recently, the use of metoclopramide was curtailed also because cisapride, another substituted benzamide, appeared to have improved efficacy and fewer side effects than the former. Unfortunately, cisapride has been removed from the market because it can cause cardiac arrhythmias. Metoclopramide has been shown to be effective in treating motility disorders in humans and, with the removal of cisapride, is being used more frequently. This author believes that sufficient support exists for the use of metoclopramide to treat POI in the horse. Additionally, some clinicians have found metoclopramide to be beneficial in the treatment of anterior enteritis that has been nonresponsive to lidocaine.

### Erythromycin

Erythromycin is a macrolide antibiotic with recognized GI side effects. When used at subtherapeutic antimicrobial levels, erythromycin stimulates gastric emptying, antroduodenal coordination, and regular spiking activity of the duodenum. Erythromycin acts as a motilin agonist, mimicking the effects of endogenous motilin on enteric smooth muscle. It also acts on enteric cholinergic neurons through serotonin (5-HT) receptors, stimulating the release of acetylcholine. Doses of 0.5 to 1.0 mg/kg added to 1 L of saline and infused over 60 minutes repeated every 6 hours have been recommended. The most common side effect is abdominal pain. Although at this drug level antibiotic-induced diarrhea should not occur, this author is aware of some reports in which diarrhea was thought to be caused by the previously mentioned dose of eryth-

romycin. Erythromycin is commonly given to humans to treat gastroparesis, and this author believes that it is a reasonable choice for treatment of proximal GI motility problems in the horse. It has also been used to treat cecal impactions.

### Lidocaine

Intravenous (IV) lidocaine has been shown to shorten the duration of paralytic ileus in humans after abdominal surgery. Lidocaine suppresses activity of afferent neurons in the bowel wall, which are thought to be involved in mediating sympathetic reflex inhibition of gut motility. Lidocaine is thought to have antiinflammatory properties through inhibition of prostaglandins, inhibition of granulocyte migration, and inhibition of release of lysosomal enzymes. Furthermore, lidocaine can directly stimulate enteric smooth muscle. Lidocaine (bolus of 1.3 mg/kg followed by 0.05 mg/kg/min for 24 hours) was found to be moderately effective in treating equine ileus, including POI and ileus associated with anterior enteritis. Side effects are muscle fasciculations and ataxia. Lidocaine should not be used simultaneously with cimetidine or metronidazole because these drugs may potentiate lidocaine's toxic effects.

According to this author's impression, lidocaine is currently the most commonly used drug to treat POI and other motility disturbances. In the author's clinic, postoperative small intestinal cases are routinely started on lidocaine prophylactically. Additionally, it is used to treat horses with anterior enteritis to decrease both intestinal inflammation and pain. The author is also aware of clinicians who use lidocaine to treat horses with colitis. Besides the clinical support for its beneficial actions on these

motility disturbances, the minor side effects make lidocaine an attractive choice as a prokinetic.

### SUMMARY

Much speculation exists concerning the indications for the use of prokinetics in treating motility disorders. At best the drugs are only moderately effective in helping to restore normal motility patterns in certain cases. They should be used only to supplement appropriate supportive therapy, such as nasogastric decompression, antimicrobial and antiinflammatory therapy, and fluid and electrolyte replacement.

### Supplemental Readings

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## CHAPTER 3.9

# Parenteral Nutrition for Colic Patients

SUSAN J. HOLCOMBE  
*East Lansing, Michigan*

**T**he most common indication for parenteral nutrition in horses is an inability to safely use the gastrointestinal (GI) tract because its normal function is impaired. For example, paralytic ileus commonly occurs in postoperative colic patients and completely prevents the use of oral nutrition. Horses that have had small intestinal resection or moderate-to-severe small intestinal distention, or proximal duodenitis/jejunitis, or horses with endotoxemia or sepsis are at risk of developing ileus and may need to be fed parenterally. The postoperative equine patient that is unable to eat is in a catabolic state,

depletes energy stores quickly, and uses body proteins for energy production. Therefore the fundamental goal of parenteral nutrition in postoperative colic patients is to provide daily nutritional requirements intravenously. In human patients and animal studies, parenteral nutrition has been found to improve wound healing, minimize muscle protein loss, decrease the weight loss usually seen in catabolic patients, and bolster immune function in patients that cannot tolerate oral nutrition. Components used in formulating parenteral nutrition include protein in the form of amino acids, carbohydrates in the form of dex-

romycin. Erythromycin is commonly given to humans to treat gastroparesis, and this author believes that it is a reasonable choice for treatment of proximal GI motility problems in the horse. It has also been used to treat cecal impactions.

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depletes energy stores quickly, and uses body proteins for energy production. Therefore the fundamental goal of parenteral nutrition in postoperative colic patients is to provide daily nutritional requirements intravenously. In human patients and animal studies, parenteral nutrition has been found to improve wound healing, minimize muscle protein loss, decrease the weight loss usually seen in catabolic patients, and bolster immune function in patients that cannot tolerate oral nutrition. Components used in formulating parenteral nutrition include protein in the form of amino acids, carbohydrates in the form of dex-

trose, and lipids in the form of long-chain fatty acids, plus electrolytes, minerals, trace elements, and vitamins.

### NUTRIENT METABOLISM IN HEALTH AND DISEASE

Carbohydrates are the primary energy source used by healthy horses. Trauma from surgery, sepsis, hemorrhage, and shock can initiate a catabolic response, causing increased energy needs but also impaired use of fuel sources. Horses may become glucose-intolerant and insulin-resistant. They preferentially oxidize lipids and catabolize protein for fuel. Additionally, horses with ileus are denied oral nutrition. Therefore these animals are at risk of developing muscle weakness and wasting as a result of catabolism of muscle protein for energy, depressed immune function, multiple organ dysfunction, GI dysmotility and mucosal atrophy, and delayed wound healing.

The body responds differently to simple starvation than to starvation accompanied by the stress of surgery and illness. In healthy horses, periods of starvation not associated with illness or injury are accompanied by neuroendocrine changes within the body that lower the metabolic rate, resulting in a decrease in nutrient needs that facilitates survival. Insulin activity decreases, and glucagon activity increases. Catecholamines and hormones associated with stress are down-regulated, which lowers the metabolic rate. During these brief periods of inappetence, hepatic glycogenolysis, and gluconeogenesis maintain the blood glucose concentration. Glycogen stores are depleted quickly, and fatty acids become the primary energy source. Glucose-dependent tissues, such as the brain and erythrocytes, cannot use fatty acids initially, so hepatic gluconeogenesis using amino acids as substrates continues. With time the horse's body adapts to using ketone bodies derived from fatty acid metabolism for energy. The protein required for cardiac and respiratory function and enzyme activity is conserved. Resting energy expenditure is decreased because of a decreased metabolic rate and changes in some hormonal levels. These adaptations prolong survival until feeding resumes.

The effects of food deprivation in stressed catabolic animals are considerably different from those observed in healthy animals. The resting metabolic rate is increased instead of decreased; protein conservation does not occur because protein becomes the principal fuel source. These effects are approximately proportional to the severity of disease. Some of the neuroendocrine changes that occur in these hypercatabolic patients include increased sympathetic nervous system stimulation and increased production of catecholamines leading to increased metabolic rate. Glucagon, glucocorticoids, and antidiuretic hormone are increased, causing relative insulin resistance, increased protein catabolism and nitrogen loss, and ultimately, more rapid development of malnutrition. A marked reduction in total body protein synthesis occurs because amino acids are used for energy. In summary, these horses have increased metabolic demands and are in a catabolic state, develop insulin resistance and glucose intolerance, preferentially use protein for fuel, become weak, have poor wound healing and incompetent immune function, and lose weight. Therefore nutritional support is mandatory.

### DETERMINATION OF ENERGY REQUIREMENTS

Energy requirements should be calculated according to the size, age, condition, and metabolic stress of the horse. The daily energy expenditure is expressed as the basal energy expenditure, which is the heat production of basal metabolism in the resting and fasted state. Maintenance requirements for healthy adult horses are estimated to be 35 to 40 kcal/kg every 24 hours or about 18,000 kcal/day. This level of nutrition has been shown to maintain body weight in healthy adult horses standing in stalls. Foals have much higher caloric requirements of approximately 120 to 150 kcal/kg every 24 hours. No good estimates exist of increased requirements in horses after surgery, trauma, hemorrhage, or burns, so this information is extrapolated from humans. Adjustments in caloric requirements include 1.1 times the basal metabolic requirements for each degree Celsius above the normal body temperature. Reports evaluating metabolic rates in critically ill humans indicate that their metabolic rates are increased over their resting energy requirements by 25% to 35% postoperatively; 35% to 50% with trauma; 50% to 70% with sepsis; and greater than 100% with head trauma or burns. Therefore in the postoperative period, a 450-kg horse after small intestinal resection that also may be endotoxemic requires approximately 60 kcal/kg per day or 27,000 kcal per day.

### COMPONENTS OF PARENTERAL NUTRITION

#### Energy

Carbohydrates, lipids, and proteins are sources of energy used in parenteral nutrition. One of the main objectives of providing parenteral nutrition is to conserve body proteins. The protein-sparing effect of parenteral nutrition is related directly to the protein intake and energy intake. Carbohydrates and lipids therefore are used to meet the horse's energy requirements, preventing breakdown of autologous protein for energy and allowing the administered protein to be used for wound healing and immune functions. Lipids and dextrose provide nonprotein calories—40% and 60%, respectively. The amino acid solution is used to meet protein requirements.

#### Lipids

Lipids are the most calorically dense nutrient, providing 9 kcal/g of lipid. Lipids also provide essential fatty acids. Commercial lipid emulsions contain long-chain triglycerides that are derived from either soybean oil or safflower oil. Glycerol, a carbohydrate energy source, is added to make these emulsions isotonic, and a phospholipid is added as an emulsifier. Lipids are isosmotic, so the addition of lipids to the solution decreases its tonicity and therefore decreases the risk of thrombophlebitis. The metabolic clearance of lipids involves the hydrolysis of triglycerides by lipoprotein lipase. This enzyme is present in capillary endothelial cells. Endotoxemia and gram-negative infections have been shown to result in a decrease of lipoprotein lipase levels. Bacterial endotoxin may induce macrophages and other white blood cells to release



mediators that suppress the activity of lipoprotein lipase. Clinically, this scenario is seen as intolerance to lipids and persistent lipemia and hypertriglyceridemia.

### Amino Acids

Healthy adult horses require 0.7 to 1.5 g/kg per day of protein, an amount that is likely increased in the postsurgical patient. Supplementation of the branched-chain amino acids (valine, leucine, and isoleucine) decreases trauma and sepsis-induced muscle catabolism and improves nitrogen retention. Arginine is essential for wound healing, immune competence, and promotion of a positive nitrogen balance. Glutamine is the principal metabolic fuel used by enterocytes, and lack of glutamine may be partly responsible for the atrophy of the bowel mucosa that accompanies prolonged periods of bowel rest. Glutamine is not an essential amino acid because it is produced in skeletal muscle. However, glutamine levels in blood and tissues drop precipitously in acute, hypercatabolic patients and may be considered a conditionally essential amino acid in critically ill horses after abdominal surgery. Glutamine-enriched parenteral nutrition has been shown to reduce the atrophic changes in the bowel mucosa during periods of bowel rest. Therefore glutamine-supplemented parenteral nutrition may play an important role in maintaining the functional integrity of the GI mucosa.

### Vitamins and Minerals

Antioxidant therapy is especially important in septic or endotoxemic patients after abdominal surgery, providing a rationale for vitamins C and E supplementation. Because of reported anaphylactoid or allergic reactions with intravenous (IV) administration, these vitamins should be given orally. Some of the IV multivitamin preparations can be added to parenteral nutrition. These products contain the fat-soluble vitamins A, D, and E that are solubilized in an aqueous medium, which permits IV administration. No adverse reactions have been reported after administration of these products. Vitamin C can be administered orally as 10 to 20 g of ascorbic acid once daily per 450-kg horse. Vitamin E can be supplemented orally at 500 IU once daily per 450-kg horse. The B-complex vitamins include thiamine, folic acid, pantothenic acid, and niacin. Thiamine (vitamin B<sub>1</sub>) is a component of thiamine pyrophosphate, an essential cofactor in carbohydrate metabolism. Vitamin B complex can be added to the parenteral nutrition solution at 20 to 30 ml per 450-kg horse per day.

Electrolytes can be supplemented in the IV fluids or in the parenteral nutrition solution. Deficiencies in calcium, potassium, or magnesium can be the primary cause or major contributors of ileus in postsurgical colic patients. Potassium depletion is inevitable in inappetent horses, and potassium should be added to the parenteral nutrition or IV fluids (20 to 60 mEq KCl/liter), depending on the fluid administration rate. Magnesium is necessary for the conversion of thiamine to thiamine pyrophosphate, so magnesium depletion (which is common in intensive care unit [ICU] patients) causes a functional form of thiamine deficiency. Hypomagnesemia also can cause neurologic signs, such as depression and ataxia, in addition to

hypersalivation, muscle weakness, and ventricular arrhythmias. Magnesium can be added safely to the IV fluids of nonazotemic horses at 4 ml of 50% MgSO<sub>4</sub> per liter.

### PREPARING THE PARENTERAL NUTRITION SOLUTION

Parenteral nutrition usually is administered to horses for short periods of time (3 to 10 days) as partial parenteral nutrition. Total nutritional requirements are generally not met. Lipids provide 9 kcal/g, protein 4 kcal/g, and dextrose 3.4 kcal/g. The goal is to provide approximately 30% to 40% of the calories with lipids and 60% to 70% with dextrose. A 500-ml bottle of 20% lipid emulsion contains 0.2 g/ml lipid  $\times$  9 kcal/g  $\times$  500 ml = 900 kcal. A 500-ml bottle of 50% dextrose contains 0.5 g/ml of dextrose  $\times$  3.4 kcal/g  $\times$  500 ml = 850 kcal. One liter of 10% amino acid solution contains 0.1 g/ml of amino acids  $\times$  4 kcal/g  $\times$  1000 ml = 400 kcal. Solutions composed of 5 to 8 g/kg/day of dextrose, 2 g/kg/day of amino acids, and 1g/kg/day of lipid are well-tolerated by horses.

Parenteral nutrition can be expensive. The solution can be prepared in the IV fluid bag, removing the cost of purchasing a parenteral nutrition bag and decreasing the osmolality of the solution. Parenteral nutrition should be prepared in a sterile hood if possible. The clinician should begin with a 5-L bag of sterile polyionic fluids, such as Plasmalyte, lactated Ringer's solution, or Normosol-R. A transfer set (International Win, Kennett Square, Pa.) then is attached and 1 L of fluid removed. Two 500-ml bottles of 50% dextrose (Dextrose 50%, 500 ml, Abbott Laboratories, North Chicago) are added, along with 1000 ml of 10% amino acid solution (LiposynII 20%, 500 ml, Abbott Laboratories), and 500 ml of 20% lipid (Aminosyn 10%, 2000 ml, Abbott Laboratories) using the transfer set. To avoid instability of the lipid caused by the low pH of dextrose, the dextrose and amino acids should be mixed first, followed by the lipid. If the lipid separates and does not mix into solution, the preparation should not be used. The transfer set then is removed from the fluid bag and replaced with an injection cap or a sampling site coupler (Baxter Health Care, Femur Division, Deerfield, Ill.). Next, 5 ml of multivitamin (Product #4205, American Pharmaceutical Partners, Los Angeles) or B complex vitamins is added. The formula can be prepared 24 hours in advance and kept in a refrigerator. This 6500-ml bag contains 4000 ml of polyionic fluid, 1000 ml of 50% dextrose, 1000 ml of 10% amino acids, 500 ml of 20% lipid emulsion, vitamins, and 3000 kcal (Table 3.9-1).

### ADMINISTERING PARENTERAL NUTRITION

This high-osmolality formulation was once given only into a central vein because of the risk of thrombophlebitis. Reports of successful administration via peripheral vessels are now common, and administration in horses via the jugular vein has been performed with few complications. To minimize the risk of thrombophlebitis, nontrombogenic catheters such as polyurethane catheters should be used, and the catheter should remain dedicated to the parenteral nutrition (i.e., medications and fluids are not administered through the same port). If parenteral nutrition is to be

**Table 3.9-1**  
**Suggested Formulas for Equine Parenteral Nutrition**

Formula	ADULT			FOAL	
	8 hr	16 hr	24 hr	8 hr	16 hr
Dextrose 50%	1000 ml	1000 ml	1000 ml	1000 ml	1000 ml
Lipid 20%	500 ml	500 ml	500 ml	250 ml	500 ml
Amino acid 10%	1000 ml	1000 ml	1000 ml	1000 ml	1000 ml
Isotonic fluids	4000 ml	4000 ml	4000 ml	1500 ml	1500 ml
Multi-vitamin concentrations	5 ml	5 ml	5 ml	5 ml	5 ml
Total volume	6500 ml	6500 ml	6500 ml	3750 ml	4000 ml
Rate (ml/hr)	500	750	1000	3-5 ml/kg/hr	3-5 ml/kg/hr
Bags/day	2	3	4	1	2
kcal/bag	3000	3000	3000	2200	3000
kcal/day	6000	9000	12,000	2200	3000
Cost (client)	\$166.40	\$250.00	\$332.80		

Adult: maintenance = 35-40 kcal/kg/day; 450-kg horse = 15,750-18,000 kcal/day; foal = 120-150 kcal/kg/day; 50-kg foal = 6000-7500 kcal/day.

administered after surgery, a second catheter can be placed in the opposite jugular vein or a double lumen catheter can be placed. Seven French, 20-cm, polyurethane antimicrobial double lumen catheters are available from several sources (Double-lumen 7 Fr catheter, #A1620, Mila International, Florence, Ky., and 7 Fr double-lumen catheter, #AK-17702, Arrow International, Inc., Reading, Pa.). The parenteral nutrition can be administered through the 18-g portal, whereas fluids and medications are administered through the 14-g portal. The parenteral nutrition should not be disconnected. If the horse is walked several times daily or removed from the stall for any reason, the bag of parenteral nutrition should be taken with the horse, thus decreasing the risk of contamination and sepsis at the catheter site. The fluid lines used for the parenteral nutrition should be changed every 24 hours.

Parenteral nutrition should be administered with an infusion pump. Postoperative abdominal surgery patients and horses with endotoxemia may have increased cortisol, adrenaline, and glucagon levels, resulting in glucose intolerance and hyperglycemia. Therefore administration of 25% to 30% of the calculated nutritional requirements per hour is the first step, and the administration rate is increased 25% every 6 to 8 hours to 75% to 100% of the horse's basal metabolic requirement. Urine and blood glucose should be monitored every 4 to 6 hours and serum triglycerides and blood urea nitrogen (BUN) daily. If the renal threshold of glucose (200-220 mg/dl with normal renal function) is exceeded, glucosuria and osmotic diuresis ensue. The rate of infusion then should be decreased to a tolerated level. Clearance of lipids can be impaired with gram-negative sepsis and endotoxemia. Monitoring triglycerides and the appearance of serum or plasma for lipemia is important to prevent hyperlipemia, especially in miniature horses and ponies. Protein administration should be monitored by periodic determination of BUN, which decreases if inadequate protein is provided or may increase if excessive protein is provided. Also, decreased

total protein (TP <4.0 g/dl) or decreased albumen (<3.0 g/dl) may indicate decreased protein intake. Electrolytes should be monitored at least once daily, and the horse should be weighed, if possible, each day.

Once the horse tolerates enteral feeding, the rate of parenteral nutrition administration is decreased slowly, by half every 6 to 8 hours, to prevent hypoglycemia because insulin levels are elevated in horses receiving parenteral nutrition.

### IMPORTANCE OF ENTERAL NUTRITION

Parenteral nutrition is administered or chosen only when the enteral route is not usable. "If the gut works, use it" is a phrase resulting from numerous animal and human studies that have shown that enteral nutrition is superior to parenteral nutrition in supporting organ function and improving organ blood flow, patient weight gain, and immune function principally because of its effect on the GI mucosa. One of the important features of the GI tract is the role of the intestinal epithelium as a barrier to invasion by pathogenic microorganisms. The barrier function of the bowel mucosa is maintained by the intake and processing of bulk nutrients along the digestive tract. Progressive atrophy and disruption of the intestinal mucosa accompany complete bowel rest. This effect becomes evident after just a few days and is not prevented by parenteral nutrition. Depletion of nutrients in the bowel lumen is accompanied by degenerative changes in the bowel mucosa, such as shortening of the microvilli and generalized disruption of the microvillus architecture. Translocation of bacteria across the GI mucosa has been documented during periods of bowel rest in intensive care patients and has been attributed to mucosal disruption from lack of luminal nutrients. These findings mean that enteral nutrition could help prevent translocation of bacteria and subsequent sepsis through maintenance of the functional integrity of the bowel mucosa. Therefore even

if the GI tract cannot be used to meet complete needs, small amounts of enteral feeding may be helpful.

### Supplemental Readings

Bartges JW: Identifying and feeding patients that require nutritional support. *Vet Med* 2001; 96:60-73.

Marino PL: Nutrition and Metabolism: the ICU Book, 2nd edition, pp 721-766, Williams & Wilkins, Baltimore, 1997.

Ralston SL: Clinical nutrition of adult horses. *Vet Clin North Am Equine Pract* 1990; 6:339-354.

Spurlock SL, Ward MV: Providing parenteral nutritional support for equine patients. *Vet Med* 1990; 85:883-890.

Sternberg JA, Rohovsky SA, Blackburn GL et al: Total parenteral nutrition for the critically ill patient. In Shoemaker WC (ed): *Textbook of Critical Care*, 4th edition, pp 898-907, WB Saunders, Philadelphia, 2000.

## CHAPTER 3.10

# Management of Pain and Dehydration in Horses with Colic

DANA N. ZIMMEL  
*Athens, Georgia*

**A**cute abdominal pain in the horse is one of the most common emergencies in equine practice. Despite the variety and complexities of colic, the majority of cases resolve with medical therapy. Controlling pain and correcting dehydration are fundamental in the treatment of gastrointestinal (GI) disorders.

### PAIN MANAGEMENT

Alleviation of pain is an important component in the management of colic. Any source of pain can cause ileus, and decreasing pain stops reflex inhibition of motility, which encourages normal peristalsis. The source of abdominal pain originates from distention of a viscus, tension on the root of the mesentery, or ischemia or inflammation of the GI tract. Initial methods used to control pain include decompression, analgesics, and sedatives.

### Decompression

Decompression of a distended viscus relieves pain and promotes motility. Gastric distention is caused by excess gas, feed, or fluid. Passage of a nasogastric tube relieves gastric tympany or removes reflux as a result of ileus or a small intestinal obstruction. However, gastric rupture can occur despite the presence of an indwelling stomach tube, unless frequent siphoning is performed.

Decompression of the cecum or the colon by trocharization can relieve severe gas distention but carries the risk of peritonitis. To trocharize the cecum, a 14-gauge, 5-inch needle is required and suction is desirable. The ap-

proach is through the right paralumbar fossa midway between the last rib and the tuber coxae, at the level of the ventral aspect of the tuber coxae. The site should be surgically prepared and locally anesthetized. The needle is held perpendicular to the skin and advanced until gas is detected. Suction or transrectal pressure on the cecal base can be used to evacuate gas. As the bowel decompresses, the needle tends to slide out of the cecum. The needle should be flushed with sterile saline before it is removed from the cecum to prevent contamination of the abdominal cavity or wall with cecal contents. A similar procedure can be performed to decompress the large colon. The horse should be monitored for signs of peritonitis and treated with antimicrobials accordingly.

Horses with severe gas colic have been observed to improve with a "therapeutic trailer ride." The mechanism for this response is not understood. A trailer ride for the majority of horses is not curative and if attempted should be en route to a hospital. Walking horses for short periods of time (15 to 30 minutes) can help eliminate mild gas discomfort. Excessive walking is detrimental because it exacerbates dehydration and exhausts the horse.

### Analgesics

Knowledge of the speed of onset and duration of action, potency, and side effects of the selected analgesics helps identify cases that require intensive care. Pharmacologic agents available for treatment of colic include non-steroidal antiinflammatory drugs (NSAIDs),  $\alpha_2$ -adrenergic agonists, opioids, and agents that provide sedation only

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(Table 3.10-1). Which medications to use and whether they are used alone or in combination depend on the degree of pain, health status, and age of the horse.

### Nonsteroidal Antiinflammatory Drugs

Nonsteroidal antiinflammatory drugs are effective analgesics in the treatment of acute abdominal pain. The mechanism of action is inhibition of cyclooxygenase (COX), which has two isoforms—COX-1 and COX-2. The constitutively expressed COX-1 releases prostanoids that perform “housekeeping” activities such as those responsible for mucosal cytoprotection, whereas inducible COX-2 is responsible for the release of proinflammatory prostanoids. NSAIDs provide analgesia by inhibiting the production of prostaglandins that sensitize nerve endings. The major side effects of NSAIDs include renal compromise and gastric/colonic ulceration. Inhibition of COX-1 is believed to be responsible for the toxic side effects of NSAIDs. Flunixin meglumine, phenylbutazone, and ketoprofen inhibit both COX-1 and COX-2. Carprofen and etodolac may be more selective COX-2 inhibitors, although their use for treatment of colic has not been evaluated. A single administration of an NSAID is unlikely to evoke serious side effects, but multiple doses of NSAIDs administered to dehydrated or debilitated horses can result in NSAID toxicity.

Flunixin meglumine is the current drug of choice used to treat colic in horses. The drug is administered intravenously at 1.1 mg/kg, and its onset of action is approximately 20 minutes but can be up to 2 hours. Lower doses of flunixin are used to control inflammation (0.5 mg/kg IV q12h to q8h) or endotoxemia (0.25 mg/kg IV q8h). When given intramuscularly, the time before onset of action is longer. The duration of action is 8 to 12 hours. Abdominal pain usually resolves after one injection of flunixin (1.1 mg/kg IV). Intermittent mild signs of colic, such as lying down, stretching out, and flank-watching despite administration of flunixin, indicate that a more serious problem is present and warrant additional diagnostics and therapy. Most lesions that require surgery become painful despite administration of flunixin; however, the clinical signs may be muted compared with the initial display of pain.

Ketoprofen is an NSAID that has not been used widely to treat horses with colic but appears to have analgesic effects similar to flunixin at a dose of 2.2 mg/kg intravenously every 24 hours. The onset of action for ketoprofen is 15 minutes. Phenylbutazone is an NSAID predominantly used to treat musculoskeletal pain. It provides fair analgesia for visceral pain and is used to treat laminitis associated with colic. Use of phenylbutazone in conjunction with other NSAIDs results in an increased risk of NSAID toxicity.

**Table 3.10-1**  
**Analgesics and Sedatives Used to Treat Colic**

Drug	Dosage	Comments
<b>NSAIDs</b>		
flunixin meglumine	0.25-1.1 mg/kg IV, IM q24h to q8h	Excellent analgesia
phenylbutazone	2.2-4.4 mg/kg IV, PO q24h to q12h	Fair analgesia
ketoprofen	2.2 mg/kg IV q24h	Analgesia similar to flunixin
carprofen	0.7 mg/kg IV, PO q24h	Selective COX-2 inhibitor
<b><math>\alpha_2</math>-Adrenergic Agonists</b>		
xylazine	0.2-1.1 mg/kg IV, IM prn	Excellent analgesia and sedation; causes ileus and hypotension
detomidine	10-40 $\mu$ g/kg IV, IM prn	100 $\times$ more potent than xylazine; causes ileus and hypotension
<b>Opioids</b>		
butorphanol	0.02-0.1 mg/kg IV, IM q3-4h; not to exceed 48 hours	Good analgesia; best when combined with $\alpha_2$ -adrenergic agonist; causes ileus
butorphanol infusion	23.7 $\mu$ g/kg/h for 24 hours	Good analgesia; fewer GI side effects
morphine	0.1 mg/kg qs to 30 ml saline for epidural injection	Preservative-free morphine recommended; onset of action 20 min; duration of action 8-16 hours
<b>Sedatives</b>		
acepromazine	0.02-0.04 mg/kg IV, IM q24h to q6h	No analgesia; causes hypotension; avoid use in hypovolemic patients
chloral hydrate	22-60 mg/kg IV slow as a 12% solution, titrated	Onset of action 15-20 min; duration of action up to 12 hours

IV, Intravenous; IM, intramuscular; q24h, every 24 hours; PO, by mouth; COX-2, cyclooxygenase-2; prn, as needed; qs, sufficient quantity; GI, gastrointestinal.

Carprofen and etodolac are the only potential COX-2 inhibitors that have been used in the horse. Carprofen at 0.7 mg/kg by mouth every 24 hours is an effective analgesic for musculoskeletal pain and has been used to treat laminitis in horses with concurrent right dorsal colitis. Information regarding the use of carprofen as treatment for colic is limited. Etodolac has been used experimentally for horses with colic and may be a valuable treatment after further investigation.

### ***$\alpha_2$ -Adrenergic Agonists***

For immediate control of severe abdominal pain,  $\alpha_2$ -adrenergic agonists provide excellent analgesia, sedation, and muscle relaxation. Xylazine and detomidine are the most commonly used drugs in this category. The analgesia is more potent, and onset of action is more rapid compared with NSAIDs. The short duration of action (20-60 min) of xylazine (0.2-1.1 mg/kg IV) is preferred for the initial examination. Detomidine (10-40  $\mu$ g/kg IV) is 100 times more potent than xylazine and lasts 40-120 minutes. Detomidine should be used with caution because its potency can mask a serious surgical lesion. For horses that need to be hospitalized and that are in a lot of pain, detomidine combined with butorphanol provides adequate analgesia and sedation for safe transport.

The major side effects of  $\alpha_2$ -adrenergic agonists are transient hypertension followed by hypotension, bradycardia, and ileus. When several doses are administered to control pain, vital signs should be monitored frequently and fluid therapy provided for cardiovascular support. Hypotension and ileus last longer than the sedative and analgesic effects. Using the lowest dose necessary to control pain and combining  $\alpha_2$ -adrenergic agonists with opioids can minimize ileus and hypotension.

### ***Opioids***

Opiate analgesics exert their effect centrally or on the spinal cord. Butorphanol is a mixed agonist-antagonist and provides the best pain relief with minimal side effects. It provides superior visceral analgesia compared with NSAIDs; however, it is not as potent as  $\alpha_2$ -adrenergic agonists. A bolus intravenous (IV) injection of butorphanol (0.02-0.1 mg/kg) can cause central nervous system (CNS) excitation and decrease GI motility. To minimize the excitatory locomotor effects, butorphanol is best used in combination with  $\alpha_2$ -adrenergic agonists. For immediate pain relief and restraint, 5 to 10 mg intravenously (450- to 500-kg horse) combined with 100 to 200 mg of xylazine provides good analgesia and sedation. Compared with an IV bolus, a continuous infusion of butorphanol (23.7  $\mu$ g/kg/hr) induces fewer GI side effects while providing analgesia.

Morphine is a pure opioid agonist that can cause excitation in the horse and decreased GI motility, disadvantages that decrease its usefulness in the treatment of colic. Judicious use of epidural morphine can provide an adjunctive method of pain control for small colon impactions, especially when surgery is not an option. Epidural administration of morphine provides analgesia within 20 to 40 minutes after injection. The duration of analgesia is 8 to 16 hours. Epidural morphine does not cause CNS excitation. Side effects are rare and include pruritus and constipation

with repetitive dosing. Preservative-free morphine should be used at a dose of 0.1 mg/kg. The location for the epidural is between the first and second coccygeal vertebrae. This site is cranial to the tail hair and can be palpated as a depression when the tail is moved up and down. The site should be clipped and scrubbed and a lidocaine bulla placed over the area for injection. An 18- to 20-gauge spinal needle is inserted at a 60-degree angle to the horizontal plane. A small amount of air should be injected easily without resistance. The morphine is diluted in 30 ml of saline and given slowly. Cases chosen for this treatment should be closely monitored.

### ***Sedatives***

Chloral hydrate is a powerful and safe hypnotic sedative. It is an alternative to  $\alpha_2$ -adrenergic agonists, providing a longer duration of action without causing hypotension or ileus. Chloral hydrate should be used in combination with an analgesic, such as an NSAID. It is best used for horses that experience pain associated with gas distention. This drug is used when surgery is not an option or when the diagnosis is obvious. Specific examples include small colon impactions, severe gas distention of the large colon, cecal impactions, and enterocolitis. The recommended initial dose is 22 mg/kg intravenously (10 grams for a 450-kg horse). Chloral hydrate should be administered as a 12% solution IV slowly (over 5 minutes) or orally. Administration through a catheter is preferred because the drug causes severe tissue injury if given perivascularly. The onset of action is 15 to 20 minutes when administered intravenously, and the duration of action is up to 12 hours but varies. If the pain returns within 30 minutes of the initial dose, half the original dose is given. The dose may be increased in increments of 5 g. Titration of the dose is often required in horses with severe pain. Redosing in 6 to 8 hours is acceptable.

## **MANAGEMENT OF DEHYDRATION**

The goal of fluid therapy is to restore circulating volume and correct electrolyte and acid-base imbalances. Maintenance fluid requirements for an adult horse are 50 ml/kg/day, which is 25 L (6.6 gallons) of water/day for a 500-kg (1100-lb) horse. Assessment of hydration can be estimated from the capillary refill time, moisture of the mucous membranes, duration of skin tenting, packed cell volume (PCV) and total protein (TP) if available (Table 3.10-2). To calculate the fluid deficit, the percent dehydration is multiplied by the body weight. The basis of fluid therapy incorporates the amount of fluid needed for maintenance, restoration of deficits, and replacement of ongoing losses (Table 3.10-3). To increase intestinal secretions and soften feed impactions, two to three times maintenance fluids are required after dehydration has been corrected. The route and rate of fluid administration is determined by the severity of the clinical signs, diagnosis, and practicality.

### **Oral Fluid Therapy**

Administration of oral fluids through a nasogastric tube is quick, convenient, and inexpensive. Most horses with colic benefit from oral fluid therapy unless the horse has more than 2 to 3 L of nasogastric reflux or absorption is

Table 3.10-2  
Assessment of Dehydration

Clinical Sign	Mild (4% to 6%)	Moderate (7% to 9%)	Severe (>10%)
Capillary refill time	1-2 seconds	2-4 seconds	>4 seconds
Mucous membranes	Fair	Tacky	Dry
Duration of skin tenting	2-3 seconds	3-5 seconds	>5 seconds
PCV (%)*	40-50	50-65	>65
TP (g/dl)†	6.5-7.5	7.5-8.5	>8.5

\*Elevation in packed cell volume (PCV) without an elevation in total protein (TP) may suggest splenic contraction from excitement or pain.

†TP can appear normal in dehydrated horses with severe protein loss.

Table 3.10-3  
Fluid Calculation Worksheet

Factor	Formula	500-kg Horse	Amount Administered
Fluid deficit	Percent dehydration $\times$ Body weight (kg)	$500 \text{ kg} \times 7\%$	35 L
Maintenance	50 ml/kg/day	$500 \text{ kg} \times 50 \text{ ml/kg/day}$	25 L
Losses	Estimate volume of reflux/diarrhea.*	Reflux obtained = 5 L	<u>5.0 L</u>
Fluid rate	Administer one-half deficit in 1-2 hr.	$40 \text{ L} \div 2 = 20 \text{ L}$	65.0 L/day total deficit 20 L bolus in 1 hr
	Divide remaining fluid over 23 hr.	$65 \text{ L} - 20 \text{ L} = 45 \text{ L} \div 23 \text{ hr}$	2.2 L/hr for 23 hr
Bicarbonate deficit	$(24 - \text{HCO}_3) \times \text{Body weight}$ (kg) $\times 0.5$	$(24 - 15) \times 500 \times 0.5$	2250 mEq bicarbonate
	5% NaHCO <sub>3</sub> = 594 mEq/L	$2250 \text{ mEq} \div 594 \text{ mEq/L}$	4 L of 5% NaHCO <sub>3</sub>
Fluid rate for bicarbonate therapy	Administer one-half deficit in 1-2 hr.	$4 \text{ L} \div 2 = 2 \text{ L}$	2 L diluted in isotonic fluids over 2 hr
	Divide remaining fluid over 12-24 hr.	$2000 \text{ ml} \div 22 \text{ hr}$	90 ml/hr in isotonic fluids over 22 hr

\*If losses are ongoing, fluid therapy must be increased to compensate for volume lost.

impaired. However, oral fluid therapy is not adequate for severely dehydrated horses. The average equine stomach has a capacity of 8 to 10 L and empties in 20 to 30 minutes when motility is normal. Administration of 6 to 8 L (2 gallons) of water by nasogastric tube in 30-minute intervals is safe, and the practitioner should check each time for the presence of reflux. When large volumes of water are given in this manner, the fluids should be allowed to flow by gravity using a funnel.

Isotonic or hypertonic solutions less than 800 mOsm/L can be administered via a nasogastric tube without causing a shift of extracellular fluid into the GI tract. Electrolyte solutions are commercially available or can be made using table salt (NaCl), lite salt (KCl), and baking soda (NaHCO<sub>3</sub>). The daily requirements for sodium and potassium are 500 to 1000 mEq/day (29-58 g) and 250 to 500 mEq/day (18.5-37 g), respectively (Table 3.10-4). The use of free choice electrolyte water is advocated in horses

with electrolyte deficits; however, water should be available simultaneously for drinking.

### Intravenous Fluid Therapy

IV fluid therapy is the most rapid method of expanding circulating volume and correcting electrolyte and acid-base abnormalities. It is indicated in horses with endotoxic or hypovolemic shock and with impaired absorption from the GI tract. The amount of fluids required to treat hypovolemic shock can range from 30 to 50 L. Half the calculated fluid deficit should be administered in 1 to 2 hours. The remainder of the deficit, plus maintenance and ongoing losses, should be evenly divided over the next 12 to 24 hours. Large volumes of fluid can be administered rapidly with a 10- or 12-gauge jugular catheter, two 14-gauge jugular catheters, a fluid pressure bag, or a fluid pump. Large catheters and fluid administered under

**Table 3.10-4**  
**Oral Electrolyte Therapy\***

Factor	Impaction	Anorexia	Diarrhea	Maintenance
Dehydration (%)	5	6	7	
H <sub>2</sub> O deficit (L)	25	30	35	
Na deficit (mEq)	1000	1000	2000	
K deficit (mEq)	800	2100	800	
HCO <sub>3</sub> deficit (mEq)			1000	
<b>Oral Electrolyte Solution</b>				
Water (L)	7	7	7	8
NaCl (tbsp)	3.6	1	1.8	2.6
KCl (tbsp)	3.8	5	1.9	1.8
NaHCO <sub>3</sub> (tbsp)		1.3	2.6	
Osmolality (mOsm/L)	523	453	397	372
TOTAL Na (mEq)	1020	510	986	748
TOTAL K (mEq)	804	1072	402	375
TOTAL HCO <sub>3</sub> (mEq)		238	476	

\*Based on 500-kg horse.

significant pressure increases the incidence of venous thrombosis.

Isotonic fluids such as Ringer's solution, lactated Ringer's solution, Plasmalyte A, or Normosol-R are suitable for replacement of volume deficits. Hypertonic (7.2%) saline solution is very useful in the treatment of shock because it increases cardiac output by shifting intracellular fluid to the extracellular space. The dose is 4 to 6 ml/kg over 10 to 20 minutes and must be followed by two to three times maintenance isotonic fluids. Normal saline (0.9%) is acceptable for replacement of fluid deficits but causes hypernatremia, hyperchloremia, and acidosis if used for maintenance.

Colloids are indicated when the total protein or albumin concentrations are decreased to less than 5 g/dl or 2 g/dl respectively. Plasma or Hetastarch (5-10 L) can be used to increase plasma oncotic pressure.

#### **Electrolytes and Acid-Base Balance**

Clinical signs of electrolyte and acid-base imbalance may be as subtle as depression seen with acidosis, weakness associated with hypokalemia, or dramatic signs such as synchronous diaphragmatic flutter ("thumps") caused by hypocalcemia. Moderately to severely dehydrated horses should have their electrolytes and acid-base balance monitored at the onset of disease and throughout the duration of fluid therapy.

Potassium is an intracellular ion that can be low in horses with anorexia, GI reflux, or enterocolitis. Evaluation of serum potassium does not reflect total body potassium because the majority of potassium resides within the cell. If serum potassium is low in the presence of acidosis, the total body deficit is likely to be severe. Hypokalemia should be treated with 0.02 to 0.08 mEq/kg/L of KCl and should not exceed 0.5 mEq/kg/hr.

Metabolic acidosis occurs in horses with acute abdomens. When the pH is less than 7.2 or the HCO<sub>3</sub> is less

than 15 mEq/L, bicarbonate therapy is indicated. The amount needed to correct acidosis can be calculated (see Table 3.10-3), or if laboratory data is unavailable, an estimate of 1 to 2 mEq/kg is suitable. Excessive bicarbonate therapy results in hypernatremia and hyperosmolality. Half the calculated deficit should be administered over 1 to 2 hours and the remainder over 12 to 24 hours. Monitoring of blood gas analyses is recommended. Fluids that contain calcium should not be mixed with bicarbonate because it forms a precipitate.

Clinical signs associated with hypocalcemia consist of muscle fasciculations, tachycardia, ileus, and synchronous diaphragmatic flutter. Ionized calcium is the best measurement of calcium. Hypocalcemia can be treated with 23% calcium gluconate (100-500 ml in 10 L) in fluids that do not contain NaHCO<sub>3</sub>.

Hypomagnesemia can result in muscle tremors, tetany, tachypnea, ventricular arrhythmias, magnesium-induced hypocalcemia, or hypokalemia. The small intestine is the primary site of magnesium absorption. Supplementation may be indicated when small intestinal absorption is decreased or surgical resection of the small intestine is performed or based on the presence of appropriate clinical signs. Recommended dose rates for magnesium sulfate are 25 to 50 mg/kg diluted in polyionic fluid by slow infusion.

#### **ORAL LAXATIVES**

One of the most common treatments for horses with colic is mineral oil (4 L) administered through a nasogastric tube. Mineral oil lubricates ingesta but does not reverse dehydration. Other laxatives available for treatment of colic include psyllium, magnesium sulfate (Epsom salts), and dioctyl sodium sulfosuccinate (DSS; 4% solution). Psyllium (16 oz in 8 L water) is a bulk laxative used to treat sand impactions. Magnesium sulfate (0.5-1 g/kg in 8 L water) is a



cathartic laxative used to treat large colon impactions. DSS (4 to 8 oz in 8 L water) is an irritant laxative used to treat impactions. Dehydration must be corrected before laxatives are used because they could worsen dehydration.

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## CHAPTER 3.11

# Duodenitis-Proximal Jejunitis

DAVID E. FREEMAN  
*Urbana, Illinois*

**D**uodenitis-proximal jejunitis (DPJ) is a sporadic disease of horses characterized by inflammation of the proximal part of the small intestine, fluid accumulation in the stomach and small intestine, colic, and endotoxemia. Age, breed, and gender predispositions have not been established, although compared with other types of colic, most horses with DPJ are 5 to 10 years old. No strong evidence exists of seasonal or dietary influences in DPJ.

The prevalence of DPJ (also known as *proximal enteritis*, *anterior enteritis*, *gastroduodenitis-jejunitis*, *gastroduodenojejunitis*, and *hemorrhagic fibrinonecrotic duodenitis-proximal jejunitis*) has been reported to account for 3% to 22% of all colic cases caused by small intestinal diseases. Geography appears to influence the prevalence and severity of the disease, with an apparently lower prevalence occurring in California than in other parts of the United States and Europe and possibly a more severe form occurring in the southeastern United States than in the Northeast. The cause of DPJ is unknown, although *Salmonella* bacteria, *Clostridium perfringens*, and acute primary mycotoxicosis have been implicated.

### PATHOLOGY

The lesions that occur with DPJ are usually confined to the proximal half of the small intestine, including the entire duodenum, sometimes the pylorus, and a variable amount of jejunum. The affected segments are usually

mildly distended to 5 to 7 cm in diameter, with a red-dish-brown fluid. The serosa may appear normal or be dark pink, and the intestinal wall can be edematous, with hemorrhagic patches sometimes arranged in a circumferential striping pattern. The mucosa can be normal, light-red, dark-red, hemorrhagic, and even necrotic and ulcerated.

Microscopic lesions can extend from the stomach distally and range from hyperemia and edema of the mucosa and submucosa to a hemorrhagic fibrinonecrotic lesion with a variable amount of hemorrhage, neutrophil infiltration, and sloughing of villus epithelium. The process begins with congestion of vessels in all layers of the intestinal wall, followed by edema, hemorrhage, and finally necrosis in the mucosa and submucosa. Transmural extension of the necrosis can lead to peritonitis.

The liver can be moderately to markedly congested, and hepatocytes may have fine vacuolar changes in the cytoplasm. Less-common hepatic changes are bile duct hyperplasia, mild mixed mononuclear cell infiltrate in the portal triad, and even small foci of coagulative necrosis. Liver damage may be secondary to small intestinal stasis, decreased blood flow or macrophage activation from endotoxemia, or extension of the inflammatory process from the duodenum to the bile ducts. Concomitant pancreatitis in horses with DPJ has been described, and some horses with DPJ may exhibit laboratory evidence of renal damage, such as casts and protein in the urine.

cathartic laxative used to treat large colon impactions. DSS (4 to 8 oz in 8 L water) is an irritant laxative used to treat impactions. Dehydration must be corrected before laxatives are used because they could worsen dehydration.

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## PATHOPHYSIOLOGY

The factors involved in the initiation of DPJ are unknown, but the pathologic changes suggest an inflammatory process that causes gastric and intestinal stasis with fluid accumulation and distention in the proximal part of the gastrointestinal (GI) tract. The inflammatory process itself could have deleterious effects on intestinal motility and on water and electrolyte transport mechanisms and could induce a vicious cycle of events. In addition, endotoxemia could alter motility in DPJ by increasing sympathetic activity. Nitric oxide (NO) from myenteric neurons also appears to act as an inhibitory neurotransmitter to circular smooth muscle of equine jejunum and could be released from invading macrophages in inflamed small intestine.

Inflammation also can have profound effects on mucosal function. Immune cells in the lamina propria of the intestine are important sources of eicosanoids, reactive oxygen metabolites, and other mediators that can stimulate chloride secretion and inhibit sodium chloride absorption in the intestine. Most of this response is medi-

ated by activation of the enteric nervous system by cyclooxygenase (COX) products and results in fluid accumulation in the intestinal lumen. Another potential cause of diminished water and electrolyte absorption in DPJ is increased mucosal permeability through enhanced paracellular diffusion, which can develop in the inflamed small intestine in the absence of mucosal damage and can enhance absorption of bacterial products such as lipopolysaccharide (Figure 3.11-1).

## CLINICAL SIGNS

DPJ affects adult horses in a wide age range and usually occurs in horses older than 1½ years, although the presumptive diagnosis has been made in nursing foals. The hallmark of the disease is reflux of a large volume of fluid through a stomach tube in a horse that initially demonstrates signs of pain and then depression. The severity of initial pain can vary from mild to severe. The reflux can resemble normal gastric contents but is more

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Please refer to the printed publication.

**Figure 3.11-1** Mechanisms proposed to explain how the inflammatory process is perpetuated in the jejunal mucosa in horses with duodenitis–proximal jejunitis (DPJ). *FMLP*, Formyl-methionylleucylphenylalanine; *PAF*, platelet-activating factor; *LTB<sub>4</sub>*, leukotriene B<sub>4</sub>; *TXA<sub>2</sub>*, thromboxane A<sub>2</sub>; *PG*, prostaglandin; *iNOS*, inducible nitric oxide synthase; *NO*, nitric oxide; *ROMs*, reactive oxygen metabolites; *LP cells*, cells in the lamina propria. (From Freeman DE: Duodenitis-proximal jejunitis. *Equine Vet Educ* 2000; 12:415.)

typically reddish-brown to bloody and positive for occult blood. The reflux can have a wide range of pH values. The heart rate can be high (usually greater than 60 beats/min) and between 80 to 100 beats/min in severe cases. Cardiac arrhythmias in some horse have been reported, but these conditions resolve with recovery from the primary problem. Laminitis has been reported in 28.4% of horses with DPJ.

## CLINICAL PATHOLOGY

Most horses with DPJ have azotemia, most likely as a result of prerenal causes such as dehydration, hypotension, and electrolyte abnormalities. Reported abnormalities include hypocalcemia (serum total calcium <10.8 mg/dl), increased serum lactate ( $\geq 14.4$  mg/dl), increased anion gap ( $\geq 5$  mEq/L), and pH changes that range from mild acidosis (most common) to alkalosis (least common). Horses with DPJ can have lower mean plasma potassium and higher mean plasma bicarbonate concentrations than horses with small intestinal obstruction. The hematocrit and plasma total protein are elevated from dehydration, and white blood cell count can vary from leukopenia to leukocytosis. Peritoneal fluid from horses with DPJ is rarely serosanguinous, and nucleated cell count and total protein concentration increase to a lesser extent than with a strangulating obstruction. Peritoneal total protein concentration can be increased to greater than 3.5 g/dl in severe cases.

## DIAGNOSIS

Clinicians may have difficulty distinguishing among ileal impactions, strangulating obstructions, and cases of DPJ. Small intestinal strangulation obstruction can affect a horse of any age, whereas DPJ is rare in horses younger than 1½ years. Heart rate can be markedly elevated and other cardiovascular changes pronounced with both diseases, but horses with DPJ may demonstrate a fever and leukocytosis. Color and odor of gastric reflux can be similar, although the volume tends to be greater with DPJ. Impaction of the ileum may resemble DPJ clinically but has a regional distribution in the United States, with most cases occurring in the Southeast from June to November—possibly related to the feeding of horses with coastal Bermudagrass hay. Palpation of the impacted ileum per rectum is diagnostic.

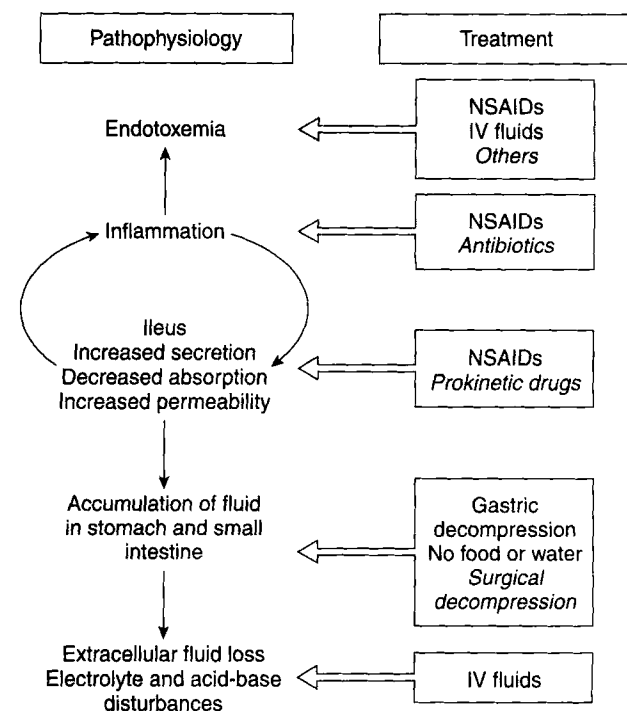
After gastric decompressions a horse with DPJ usually demonstrates relief from pain and becomes quiet, and the heart rate usually decreases, whereas a horse with mechanical obstruction will not improve. On rectal examination, the degree of small intestinal distention with DPJ is subjectively less than with ileal impaction. Peritoneal fluid is of some value in distinguishing between these diseases, with minor changes consistent with DPJ and more severe changes and serosanguineous color suggestive of strangulation.

Transabdominal ultrasonographic findings of edematous, distended, and amotile small intestine strongly suggest strangulation obstruction. With DPJ, the duodenum and jejunum are fluid-filled and have normal, increased, or diminished motility; in addition, the bowel wall has

variable thickness and a hypoechoic appearance. The distended duodenum can be imaged on ultrasound examination ventral to the right kidney at the sixteenth and seventeenth intercostal spaces on a line from the olecranon to the tuber sacrale.

## TREATMENT

The most important goals of treatment of horses with DPJ are frequent gastric decompression, correction of disturbances in water and electrolyte homeostasis, and restoration of normal intestinal function. In many cases the first two goals accomplish the latter (Figure 3.11-2). An indwelling nasogastric tube is recommended and should be capped between periods of decompression. Decompression should be attempted at least once every 2 hours and the volume recorded. In most cases, gastric fluid accumulation ceases in less than 3 days, but more severe cases may require gastric decompression for 7 days or more. Complications of prolonged nasogastric intubation are rare but include pharyngitis, esophagitis, and esophageal trauma.



**Figure 3.11-2** Manner in which recommended treatments of duodenitis–proximal jejunitis (DPJ) interrupt the proposed pathophysiologic processes and their consequences. Inflammation is proposed to be the result of an initial injury that damages the epithelium and is perpetuated by local inflammatory events to create a vicious cycle. Note that non-steroidal antiinflammatory drugs (NSAIDs) and intravenous (IV) fluids are directed against more than one process. Treatments italicized are either not necessary in every case or have a less well-defined role in treatment than others. (From Freeman DE: Duodenitis–proximal jejunitis. *Equine Vet Educ* 2000; 12:415.)

Intravenous (IV) infusion of a balanced electrolyte solution is required to restore extracellular fluid volume, correct electrolyte and acid-base balances, and maintain normal renal function, all of which are necessary for the return of normal GI function. Large volumes of fluids (as much as 100 L of fluids daily) are required in severe cases to replace lost GI fluids, and careful maintenance of large-bore jugular catheters is an essential part of treatment. Horses must be kept off food and water until the condition has resolved, which can exacerbate the electrolyte and fluid disturbances of DPJ. Additional attention should be paid to calcium and potassium levels, both of which can become depleted in horses with intestinal injury. In addition, decreased food intake can exacerbate intestinal motility abnormalities. Horses that have DPJ for several days may benefit from total parenteral nutrition. Careful balance must be sought between the volume of fluid administered and the volume lost to ensure that the horse does not become overhydrated, which may increase the volume of fluid lost into the intestinal lumen, thereby elevating the volume of reflux. Blood packed cell volume and total protein values should be used as guides to hydration status.

Nonsteroidal antiinflammatory drugs (NSAIDs) such as flunixin meglumine (Banamine) given at doses of 0.25 to 0.5 mg/kg every 8 hours can prevent or attenuate the hemodynamic responses to lipopolysaccharide, reduce lipopolysaccharide-induced increases in plasma concentrations of thromboxane and prostaglandins, inhibit the effects of lipopolysaccharide on intestinal motility, and block prostaglandin-mediated intestinal secretion. In horses with severe DPJ, the full dose of flunixin meglumine (1.1 mg/kg q12h) may be indicated, but the lower dose might prevent the potential harmful effects of prolonged NSAID use on the GI tract and kidneys, especially in dehydrated horses. Other strategies that interfere with the deleterious interaction of lipopolysaccharide with the host inflammatory system are antibodies directed against the conserved core region of lipopolysaccharide, the polypeptide antimicrobial drug polymyxin B, and pentoxifylline, a methylxanthine derivative that can reduce lipopolysaccharide-induced production of cytokines and thromboxane in horses. Use of antibiotics in horses with DPJ is controversial, but penicillin together with an aminoglycoside such as gentamicin or a third-generation cephalosporin (ceftiofur sodium [Naxcel]) can be used.

Because the dominant clinical manifestation of DPJ is accumulation of large volumes of fluid in the stomach and small intestine, treatment may include prokinetic agents. Metoclopramide may be given at a dose of 0.125 mg/kg IV or as a continuous infusion at 0.04 mg/kg/hr to prevent extrapyramidal side effects. Cisapride may also be useful, but is not readily available. Erythromycin (0.1 or 1.0 mg/kg) is a macrolide antibiotic that can hasten solid-phase gastric emptying in healthy adult horses, but its effectiveness declines with repeated use. IV lidocaine may also be useful. The recommended protocol for lidocaine in horses is an initial bolus of 1.3 mg/kg IV infused slowly during a 5-minute period, followed by 0.05 mg/kg/min in saline or lactated

Ringer's solution during a 24-hour period. Muscle fasciculations that progress to ataxia are possible complications, and the dose should be decreased at the onset of fasciculations. Prophylaxis against development of laminitis should also be considered in horses with DPJ.

Surgery is indicated when (1) a mechanical lesion (strangulating obstruction or intraluminal obstruction) cannot be ruled out satisfactorily by available diagnostic methods; (2) the horse is not responding to medical treatment; or (3) a bypass procedure is required. Reluctance to perform surgery on horses with DPJ is based on the concern that these horses do not handle the stress of anesthesia and surgery well and that surgery can reduce survival. However, many horses with mild-to-moderate signs of DPJ that undergo surgery will respond favorably to evacuation of small intestinal contents into the cecum. For refractory cases of DPJ, bypass methods described include temporary duodenocecostomy through an eighteenth rib resection, duodenojejunoscopy through a ventral median celiotomy, jejunojejunoscopy, and a side-to-side gastrojejunostomy. Obstructive adhesions can occur after abdominal surgery in horses with DPJ, especially in severe cases, with or without a bypass procedure.

## PROGNOSIS

The reported survival rates for DPJ range from 25% to 94%, and recurrence is rare. Anion gap, volume of gastric reflux, and abdominal fluid total protein concentration in the first 24 hours are useful indicators of prognosis. Some horses that do not respond to medical treatment are euthanized because the cost of continued treatment can be considerable. Laminitis is a life-threatening complication of DPJ, and its risk may be related to the severity of endotoxemia, body weight, and hemorrhagic reflux at the time of admission. Survival is lower in horses with laminitis that develop distal displacement of the distal phalanx, compared with those that have rotation only.

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## CHAPTER 3.12

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# Strangulating Obstruction of the Small Intestine

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**S**trangulating obstruction of the small intestine is often fatal because of simultaneous occlusion of the intestinal lumen and its blood supply, which results in progressive necrosis of the mucosa and development of endotoxemia. Among the more common causes of this condition are strangulating lipomas and entrapment within a natural internal opening or a mesenteric defect. Horses with this type of obstruction are widely recognized as being very susceptible to postoperative complications, most notably endotoxic shock, postoperative ileus, and intraabdominal adhesions. Despite these complications, short-term survival rates (usually defined as discharge from the hospital) have dramatically improved over the last decade. Long-term survival remains a major concern, however, particularly because of complications associated with adhesions.

### CLINICAL SIGNS

Horses with strangulating obstruction of the small intestine typically have moderate and persistent signs of colic until the later stages of the disease process, when they become profoundly depressed. Horses demonstrate progressive signs of endotoxemia, including congested mucous membranes, delayed capillary refill time, and an elevated heart rate (60-80 bpm). In addition, reflux is typically obtained after passage of a stomach tube, and loops of distended small intestine are usually detected on rectal palpation of the abdomen. However, these latter findings are variable depending on the duration and location of the obstruction. For example, horses with ileal obstructions tend to experience reflux later in the course of the disease process than horses with a jejunal obstruction. Furthermore, a horse that has an entrapment of small intestine in the epiploic foramen or a rent in the gastrosplenic ligament may not have palpable loops of small intestine because of the cranial location of these structures.

Abdominocentesis is indicated in horses with suspected strangulation of the small intestine because analysis of abdominal fluid can provide critical information on the integrity of the intestine. For instance, a horse that has signs compatible with a small intestinal obstruction and also has serosanguineous abdominal fluid with an elevated protein level ( $>2.5$  g/dl) is likely to require surgery. A horse that also has an elevated white blood cell count ( $>10,000$  cells/ $\mu$ l) in the abdominal fluid likely has extensive or long-standing strangulation.

### TREATMENT

Treatment should initially be aimed at controlling pain. Short-term analgesics such as xylazine (0.3-0.5 mg/kg IV prn) and butorphanol (0.05 mg/kg IV prn) are very useful because of their potency and because recurrent colic usually is detected within the time of the examination (30-60 min). The more potent  $\alpha_2$ -agonist detomidine (5-10  $\mu$ g/kg IV prn) is required for horses that are experiencing violent pain or pain that recurs within a brief period of time (e.g., 5-15 min). Long-term analgesics such as flunixin meglumine (1.1 mg/kg IV q12h) are very useful for more prolonged periods of analgesia and to reduce endotoxin-induced prostanoids. Flunixin meglumine is best used after short-duration analgesics, however, so that recurrent colic can be detected early. In addition, the dose interval is extremely important, given the deleterious effect of this drug on both the gastrointestinal (GI) mucosa and kidneys, particularly in dehydrated horses.

The second major goal of treatment is to ameliorate signs of shock. Horses with strangulating obstruction of the small intestine are typically at least 6% dehydrated (Table 3.12-1) and require large volumes of isotonic fluids (e.g., 30 L in a 500-kg horse) to correct fluid loss or sequestration. Half the deficit can be administered rapidly (as much as 100 ml/kg/hr) followed by a reduced rate for the remainder of the deficit volume (3-5 L/hr). To achieve more rapid correction of intravascular volume depletion, hypertonic saline or an oncotic agent such as hetastarch can be preadministered or coadministered with isotonic fluids. However, these agents do not replace the need for isotonic fluids.

Treatments aimed at reducing the effects of the endotoxin-induced inflammatory cascade include flunixin meglumine and pentoxifylline. The latter is a phosphodiesterase inhibitor that reduces elaboration of tumor necrosis factor (TNF)- $\alpha$ , although this effect is questionable at the currently recommended dosage (12 mg/kg). This drug also has rheologic effects that may reduce the onset of microcirculatory disease, including laminitis. Additional treatments that may be used, particularly if endotoxemia is detected in the early stages, are agents that bind endotoxin. These agents include hyperimmune serum (antibodies directed against the core polysaccharide of either J5 *Escherichia coli* or the Re mutant of *Salmonella* bacteria) and polymyxin B (6000 U/kg, IV).

**Table 3.12-1**  
**Physical Signs of Dehydration**

Degree of Dehydration (%)	Duration of Skin Tenting (Seconds)	Degree of Enophthalmos
Normal	2-3	None
6	4-6	None
8	6-8	Mild
10	>8	Obvious

### MECHANISMS OF MUCOSAL INJURY

A great deal of work has been done to characterize mucosal injury that occurs during strangulation and, more recently, during reperfusion. In general, the lesion that develops during strangulation is severe and leaves little viable bowel for further injury during reperfusion. The severity of the ischemic lesion is partly attributable to the fact that in most cases the initial occlusion of veins and partial occlusion of arterial blood supply during strangulation induces a hemorrhagic lesion. This process results in extensive congestion and mucosal degeneration. The bowel peripheral to the strangulating lesion may also be injured as a result of distention. In addition, the distended small intestine and bowel that remains viable after surgical correction of strangulation may sustain reperfusion injury after surgical correction of the lesion, although this occurrence has not been documented in natural cases of colic. Furthermore, attempts to reduce mucosal injury in the horse with antioxidants, which would be expected to inhibit reperfusion injury attributable to reactive oxygen metabolites, have been unsuccessful.

### CAUSES OF STRANGULATING OBSTRUCTION OF THE SMALL INTESTINE

Of the many causes of strangulating obstruction of the small intestine, strangulating lipomas are by far the most common cause observed at North Carolina State University, an institution that evaluates a disproportionately high number of small intestinal obstructions (at least 50% of the colic surgical caseload). Lipomas form between the leaves of the mesentery as horses age and develop mesenteric stalks when the weight of the lipoma tugs on the mesentery. The lipoma and its stalk may subsequently wrap around a loop of small intestine or small colon, causing strangulation (Figure 3.12-1). Strangulating lipomas should be suspected in aged (>15 years) geldings with acute colic referable to the small intestinal tract. The fact that geldings are at risk suggests an endocrine role in fat deposition and subsequent lipoma formation. Although preventive measures have not been clinically tested, specific attention to the diet of mature and aging geldings to reduce excess body fat should be considered. Ponies also appear to be at risk for the development of



**Figure 3.12-1** Intraoperative view of a lipoma (arrows) strangulating a segment of jejunum. An additional lipoma in the surgical field was not contributing to the strangulation.

strangulating lipomas—possibly because of their propensity to accumulate body fat. This tendency suggests that similar precautions should be taken in regards to the diet of ponies.

The diagnosis of small intestinal strangulation by a pedunculated lipoma is usually made at surgery, although on rare occasions a lipoma can be palpated per rectum. Treatment involves surgical resection of the lipoma and strangulated bowel, but strangulated intestine sometimes remains viable. Studies indicate that approximately 75% of horses are discharged from the hospital after surgical treatment, but the long-term survival rate (>6 months) is closer to 50%.

Entrapments within the epiploic foramen or within a mesenteric or ligamentous defect appear to be the next most common cause of strangulating obstruction of the small intestine. The epiploic foramen is a potential opening (because the walls of the foramen are usually in contact) to the omental bursa located within the right cranial quadrant of the abdomen. The foramen is bounded dorsally by the caudate process of the liver and caudal vena cava and ventrally by the pancreas, the hepatoduodenal ligament, and the portal vein.

Epiploic foramen entrapment of small intestine tends to be more prevalent in older horses, possibly because of enlargement of the epiploic foramen when the right lobe of the liver undergoes age-associated atrophy. However, the disease has also been recognized in foals. The diagnosis is definitively made at surgery, although ultrasonographic findings of distended loops of edematous small intestine adjacent to the right middle body wall suggest epiploic-foramen entrapment. Entrapped small intestine may enter the foramen from the visceral surface of the liver toward the right body wall, or the opposite direction. Studies differ as to which is the most common form of the disease. In epiploic foramen entrapment treatment, the epiploic foramen must not be enlarged either by blunt force or with a sharp instrument, as rupture of the vena cava or portal vein and fatal hemorrhage may occur. Prognosis has substantially improved over the last decade, with current short-term survival rates of approximately

75%. However, studies indicate that long-term survival may be as low as 60%.

Recent studies on small intestine entrapment within mesenteric defects indicate that this form of colic carries a particularly poor prognosis stemming from the clinician's inability to reduce the intestinal obstruction, severe hemorrhage from the mesentery, or an excessive length of involved intestine (>50% of the length of the small intestine). In addition, other types of mesenteric or ligamentous defects that entrap small intestine continue to be discovered. For example, a recent report documents small intestine entrapment in a defect in the proximal aspect of the cecocolic ligament in nine horses, with a long-term survival rate of approximately 50%.

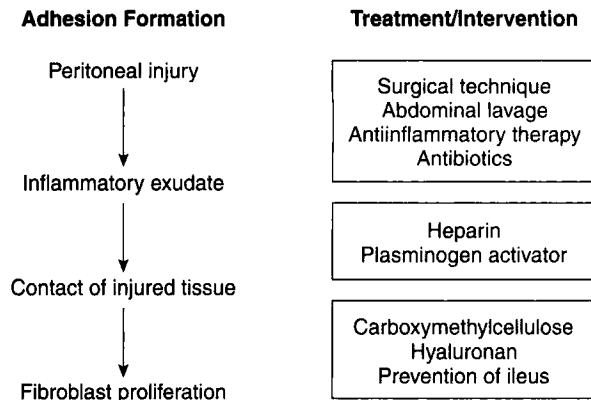
## POSTSURGICAL COMPLICATIONS

Complications that limit survival include postoperative ileus and intraabdominal adhesions. The prevalence of postoperative ileus appears to be decreasing, possibly as a result of early referral or improved surgical technique in horses with strangulating obstruction of the small intestine. Early return to feeding of horses after small intestine surgery has been advocated as a means to stimulate motility. For example, horses that have reduced signs of endotoxemia and a brighter attitude at 24 hours after surgery may be given a handful of good-quality alfalfa, followed by incremental increases in feed intake after the first defecation. Onset of postoperative ileus is most readily detected by a sudden elevation in heart rate. Some clinicians believe that a stomach tube should be left in place during the early postoperative period. However, to reduce the risk of esophageal and stomach irritation, placing a tube only when needed seems more reasonable.

Postoperative adhesions are suspected in horses exhibiting intermittent colic beginning 3 to 5 days after surgery. Postoperative colic dramatically lowers the survival rate in horses after small intestine resection. Methods to reduce the prevalence of adhesions (Figure 3.12-2) remain controversial but include physical barriers to adhesion development (hyaluronic acid membranes and carboxymethylcellulose gel), antiinflammatory medication (flunixin meglumine, 0.25-0.5 mg/kg IV q8-12h), and anticoagulant administration (heparin, 40 U/kg, q12h SQ for 48 hours). Close monitoring of the hematocrit is warranted in horses receiving heparin because this agent induces red blood cell agglutination. In addition, the patient should be observed closely for any signs that indicate a clotting disorder (such as excessive bleeding at a venipuncture site or the abdominal incision). Adhesions that cause a clinical problem occur in approximately 20% of horses after colic surgery and are most likely to cause a problem within the first 2 postoperative months. This information is particularly helpful to owners, who frequently ask when they can expect their horses to be healthy again. Although horses that have had surgical correction of colic are always at greater risk of complications than horses that have not had surgery, the prevalence of complications is greatly reduced after 2 months.

## PROGNOSIS

The prognosis for survival in horses with strangulating lesions of the small intestine is an approximately 75%



**Figure 3.12-2** Pathway through which intraabdominal adhesions are formed and associated interventions or treatments that may interrupt the adhesion pathway.

short-term survival rate and a 40% to 70% long-term survival rate, depending on the horse's condition. Owners should be alerted to the reduced long-term survival rate compared with the short-term survival rate so that they do not harbor unrealistic expectations. The prognosis can be amended on the basis of severity of endotoxemia at presentation (heart rate being the most consistently important prognostic indicator) and extent of strangulation at surgery. Although horses have demonstrated the ability to survive after resection of 50% to 70% of the small intestine, these horses often have more severe signs of endotoxemia, possibly because of the surface area of compromised mucosa that limits survival. A recent preliminary study on resection of the small intestine in horses has revealed that horses that exhibit clinical signs of endotoxemia for 3 days or longer were far less likely to survive to discharge than horses that had resolution of such signs within 24 to 48 hours.

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## CHAPTER 3.13

# Ileal Impaction

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Ileal impaction is the most frequently reported cause of nonstrangulating obstruction of the small intestine in adult horses and is seen predominantly in the southeastern United States. This condition is most likely associated with the feeding of coastal Bermudagrass hay harvested in tall stands or late summer cuttings. The lignin and crude fiber content of this hay increases markedly in these conditions and substantially decreases the digestibility factor. Differentiating ileal impactions from strangulating obstructions and duodenitis/proximal jejunitis with adynamic ileus may be difficult. In retrospective studies of acute abdominal disease, ileal impaction has been reported to have a prevalence of 0.5% to 10.8%.

### ANATOMY AND PHYSIOLOGY

The ileocecal junction is situated in the right dorsal quadrant of the abdomen; because of the short mesenteric attachments to the cecum and right dorsal colon, the junction is relatively immobile. The ileal orifice is partially inverted into the cecum, thereby placing the orifice in the center of a slight elevation formed by an annular fold of mucous membrane that contains a network of veins. The network of veins and the muscle coat of the ileum serve as a functional ileal sphincter. When the ileum is relaxed, it is difficult to distinguish from the jejunum. In contrast, when the ileum contracts it can be easily distinguished from the jejunum by its thicker muscular wall and narrow lumen.

Liquid digesta is rapidly propelled through the ileum into the cecal base, moved to the cecal apex, mixed with cecal contents, and then propelled into the right ventral colon. The migration action potential complex (MAPC) is a prominent myoelectric complex and is a normal event in the equine ileum but has not been recognized in the equine jejunum. These motility patterns are stimulated by the presence of liquid digesta and are responsible for its aboral transport. Data suggest that the MAPC rather than other migrating myoelectric complexes of the ileum may be responsible for the transit of digesta through the ileum into the cecum and is the only ileal event related to cecal motility patterns. Although the cranial and caudal aspects of the cecal base are capable of generating independent retrograde (base to apex) spiking activity, this activity also may in part be initiated by the MAPC of the ileum. Thus ileal and cecal filling may be more important in regulating ileocecal motility events than are the nervous or endocrine stimuli associated with eating.

Because the progressive myoelectric activity from the cecum to the right ventral colon is initiated from an electrical pacemaker near the cecal apex, surgically removing

or bypassing the ileum does not adversely affect the motility of the large intestine. However, bypassing the ileocecal valve disrupts the normal MAPC progression from the ileum to the cecum and right ventral colon and may allow bacterial overgrowth within the small intestine, resulting in mucosal cell damage. Therefore the ileocecal orifice should be preserved if possible.

### ETIOLOGY

Ileal impactions occur most commonly in the southeastern United States and in Europe. The cause of ileal impactions is unknown, although feeding horses hay with high fiber content has been associated with ileal impaction in the United States. Coastal Bermudagrass hay—which is often dry, fine, and populated with many stems—is commonly fed to horses in the southeastern region of the United States. When coastal Bermudagrass pastures mature (as seen in tall stands or late summer cuttings), the lignin and crude fiber content increases markedly. When the mature grass is cut and fed as hay, the additional fiber can result in a predisposition to impaction colic, a condition that is aggravated further by a combination of hot, stressful conditions; limited consumption of digestible roughage; ingestion of pelleted feeds; and limited twice-daily feeding patterns. Ileal impactions have a low incidence rate in other parts of the United States, where legume or other hay combinations are the primary sources of roughage.

A significantly higher risk for ileal impaction in horses exists in the southeastern United States during the fall season (September–November). Several possibilities exist for the apparent association between time of year and ileal impaction. An increased feeding of cured hays occurs in the southeastern United States as pastures become sparse from long, hot, and dry summers and the onset of cooler weather. Changes in the nature of the hay available at this time of year (higher lignin and crude fiber content) and changes in feeding practices may alter intestinal motility patterns. In addition, changes in the metabolic activity of the intestinal microflora also can occur with an altered feeding pattern to induce ileal impaction. These alterations may result in impaction colic disorders, especially if they are associated with decreased water consumption. An outbreak of ileal impaction in seven horses associated with the recent introduction of coastal Bermudagrass hay, where the horses had limited water intake because of cooler temperatures, has been described.

In Europe, ileal impactions are primarily idiopathic in nature and associated with vascular thrombotic disease.

Verminous arteritis caused by *Strongylus vulgaris* larvae occurs most frequently in the ileal branch of the cranial mesenteric artery. When *S. vulgaris* larvae penetrate the ileal mucosa and migrate in the submucosa, ileal migrating myoelectric complex spike activity decreases and MAPC frequency increases. This increase in MAPC frequency indicates that a relationship may exist between *S. vulgaris* larval infection and spasmodic colic seen in horses. Most or all of the responses to live L<sub>3</sub> larvae may have little to do with penetration and migration into the wall of the ileum but may be caused by elaboration of chemical agents by the larvae. Disruption of normal ileal motility occurs when the larval antigens are present in the ileal lumen. These lesions further predispose the ileum to episodes of hypoperfusion and segmental atony. The ileum's blood supply and fixed nature within the intestinal tract may be important reasons why the ileum is affected by obstructive disease more frequently than the rest of the small intestine.

*Anoplocephala perfoliata* is pathogenic for horses because heavy burdens of the parasites may be associated with severe histologic changes at the ileocecal junction. Several clinical reports have linked tapeworm infections with intestinal diseases in horses, including ileal thickening, obstruction and intussusception, and colonic volvulus. In addition to macroscopic thickening of the ileocecal valve, morphometric analysis of the mucosa reveals that in horses with more than 100 tapeworms the mucosa is significantly thicker than that of healthy horses. The mucosa and submucosa are infiltrated with eosinophils. The severity of these changes at the ileocecal junction supports the view that appropriate anthelmintic treatment for tapeworms would be beneficial in minimizing lesions in the ileum.

Hypertrophy of the muscular layer of the ileum produces luminal narrowing and partial obstruction. Muscular hypertrophy occurs in two forms—idiopathic (primary) and compensatory (secondary). With idiopathic hypertrophy, no detectable stenosis of the distal intestine occurs to cause the proximal intestinal muscularis to hypertrophy. With the compensatory form of muscular hypertrophy, the muscular layer of the small intestine hypertrophies in response to chronic distal intestinal stenosis. The hypertrophied muscle narrows the intestinal lumen, causing partial obstruction and distention of the intestine proximal to the obstruction, which causes abdominal pain. A common historical finding is partial anorexia and chronic weight loss of 1 to 6 months' duration. Exploratory celiotomy is the only definitive method used to diagnose ileal muscular hypertrophy as a cause of colic. Full-thickness rupture of the ileum with subsequent diffuse, septic peritonitis has been reported in horses with idiopathic muscular hypertrophy.

Trauma to the body wall can result in abdominal wall hernias in which an ileal impaction can develop subcutaneously. Ileal impactions associated with internal hernias involving mesenteric rents or the epiploic foramen, incarcerated scrotal-inguinal hernias, and intraabdominal adhesions are usually complicated by the incarceration of small intestine.

## CLINICAL SIGNS

Impaction of the ileum initially causes abdominal pain as a result of small intestinal distention and spasm at the site

of impaction. Abnormal intestinal contractions extrude water from the accumulated mass of ingesta to create a drier, firmer, obstructing mass. Because fluid losses are minimal, few systemic effects arise during this stage of the condition. Proximal to the obstruction of the intestine, absorption of water is impaired and secretion of fluid is increased, resulting in loss of fluid into the intestinal lumen. The pain becomes more severe as the intestine proximal to the impaction distends with gas and fluid. The reduction in circulatory function arises secondary to dehydration caused by the sequestration of fluid in the intestine, insensitive metabolic fluid loss, and a reduced oral intake of fluid. Progressive deterioration in circulatory function with concurrent intestinal distention is associated with a decrease in survival.

## DIAGNOSIS

Impactions of the ileum may be detected on transrectal palpation of the abdomen and are typically located in the mid-abdomen adjacent to the cecum, with limited mobility of the impacted intestine in the abdominal cavity (Figures 3.13-1 and 3.13-2). Because of complete intraluminal obstruction of the ileum, distention of the small intestine develops early in the course of the condition, which prevents successful palpation of the impaction in many cases. Therefore an impaction of the ileum can be most readily identified when examination is performed before onset of distention of the small intestine. As a result of excessive distention of the small intestine, ileal impactions were identified by transrectal examination in only 12 of 93 horses in two retrospective studies.

An increased heart rate (>60 bpm), nasogastric reflux, and decreased intestinal sounds are additional signs of impaction of the ileum. The packed cell volume (PCV), plasma protein, serum anion gap, and protein concentration in the peritoneal fluid are usually increased. In contrast, the white blood cell count, serum urea nitrogen, sodium, potassium, chloride, and peritoneal fluid white blood cell count are normal. A mild metabolic acidosis is usually present. Significant differences in anion gap and plasma protein concentration have been reported between survivors and nonsurvivors of ileal impaction, with higher values reported for nonsurvivors. These findings, although variable for individual cases, are indicative of a nonstrangulating obstruction of the small intestine. Gastric reflux on nasogastric intubation and the presence of small intestinal distention on rectal examination are consistent with small intestine obstruction or proximal enteritis, although other diseases infrequently cause these clinical findings. Peritoneal fluid analysis can help to differentiate simple obstruction from strangulating obstruction of the small intestine. Abnormal findings in peritoneal fluid occur earlier in the course of the obstruction with strangulation obstruction than with simple obstruction.

## TREATMENT

Successful medical treatment of horses with ileal impactions may be facilitated by a combination of intravenously administered fluids, sedatives, analgesics, or nonsteroidal antiinflammatory drugs (NSAIDs). Goals of initial management of horses with ileal impaction colic

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**Figure 3.13-1** Structures that can be identified during rectal examination of a normal horse: small colon with distinct fecal balls (1); cecal base containing some gas (2); cecal ventral taenia band (3); spleen (4); kidney (5); renosplenic ligament (6); aorta (7); cranial mesenteric root (8); pelvic flexure and parts of left large colon (9). The ileum normally cannot be palpated and therefore was not included in this illustration of normal rectal findings. (From Hanson RR, Baird AN, Pugh DG: Ileal impaction in horses. *Comp Cont Educ Pract Vet* 1995; 17:1287.)

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**Figure 3.13-2** Structures that can be identified during rectal examination of a horse with ileal impaction: enlarged ileum containing doughy ingesta (1); ileocecal orifice (1'); distended loops of small intestine, fluid-filled or tympanic without thickening of the bowel wall (2); cecal ventral taenia band (3); spleen (4); kidney (5); renosplenic ligament (6); aorta (7); cranial mesenteric root (8); pelvic flexure and parts of left large colon (9). (From Hanson RR, Baird AN, Pugh DG: Ileal impaction in horses. *Comp Cont Educ Pract Vet* 1995; 17:1287.)

are pain control, reduction of intestinal spasm in the area around the impaction, hydration of the patient and luminal contents to allow passage of ingesta, and restoration of normal intestinal function. Ileal impactions may resolve spontaneously with aggressive medical therapy. The most useful indicators for separation of surgical from nonsurgical candidates are deteriorating cardiovascular status, the persistence of abdominal pain after nasogastric decompression, poor response to analgesic drugs, and progressive distention of loops of small intestine as evaluated on transrectal examination.

With the current state of knowledge about this disease, surgery is now performed only on horses with signs of progressive abdominal disease and unrelenting pain. Retrospective studies have shown that the mean duration of clinical signs before surgery ranges from 13 to 17 hours for survivors and 18 to 25 hours for nonsurvivors. Progressive deterioration of the horse's circulatory function, combined with progressive intestinal distention, are primary reasons for the decrease in survival rate, with increasing time from onset of the condition to surgical intervention. Therefore early surgical intervention with



**Figure 3.13-3** Impaction of the ileum revealed during exploratory celiotomy. The impaction was caused by occlusion of the lumen with coastal Bermudagrass hay.

these associated clinical signs may decrease mortality and postsurgical complications associated with this disease.

If surgical intervention is indicated, extraluminal massage of the impaction (Figure 3.13-3) and passage of ingesta into the cecum should be considered as the desired means of correction because of the less successful results associated with bypass procedures. Direct infusion of the impaction with 60 ml of dioctyl sodium sulfosuccinate diluted in 1.5 L of saline or direct infusion of 500 ml of carboxymethylcellulose may soften the obstruction to allow gentle massage to mix and extrude the ingesta through the ileocecal orifice. It is important to note, however, that excessive manipulation of the small intestine may cause serosal damage and predispose the horse to adhesion formation. Because of the potential for this serious complication, carboxymethylcellulose is also applied to the serosal surface of the ileum and the surgeon's hands to decrease trauma associated with manipulation of the impaction. Once the ileal contents have been moved into the cecum, the ileum and ileocecal valves are usually edematous and moderately thickened because of the previous obstruction. Unless the thickening is thought to involve the muscular portions of the ileum or is severe, bypass procedures are not performed, thus minimizing postoperative complications.

Ileal impactions have been previously associated with muscular hypertrophy of the ileum and ileal dysfunction. As a result, jejunocecostomies have been routinely performed to prevent reimpaction of the ileum. Except in cases in which hypertrophy of the muscular layers or ileal ischemia is suspected, jejunocecostomy has been abandoned. If muscular hypertrophy of the ileum is present with associated ileal dysfunction, then a bypass between

the distal jejunum and cecum without ileal resection should be created to prevent recurrence of the impaction; this procedure ensures the passage of ingesta and preserves the original anatomic conformation. Although feed material may still attempt to pass through the ileum and potentially create abdominal pain, clinical case surveys suggest that postoperative morbidity and mortality are lower after this procedure than if a resection and anastomosis is performed. Intestinal resection should be reserved for those horses with small intestinal obstruction compounded by intestinal ischemia.

## PROGNOSIS

Successful medical therapy of horses with ileal impaction is facilitated by an accurate early diagnosis of the disease. Softened ileal impaction, improved cardiovascular status, reduced signs of abdominal pain, decreased amounts of gastric reflux, and decreased distention of loops of small intestine during repeated transrectal examinations indicate a positive response to medical treatment. Previous retrospective studies have reported that 39%, 55%, 64%, and 95% of horses in which an ileal impaction was diagnosed by an exploratory celiotomy survived long-term (5 months to 6 years). Reasons for death or euthanasia include ileus, shock, impaction, gastric rupture, laminitis, intestinal adhesions, jejunal incarceration, and/or peritonitis. A majority of these complications and the corresponding increased mortality are the result of complications associated with the intestinal resection or bypass procedures. Reimpaction of the ileum after manual reduction can occur, however. Although ileus is a common complication of abdominal surgery, no difference has been reported in the occurrence of postoperative ileus for survivors and nonsurvivors.

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## CHAPTER 3.14

# Large Colon Impaction

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### EPIDEMIOLOGY AND ETIOLOGY

Large colon obstruction is frequently caused by impaction. Dehydrated or densely packed ingesta accumulates orad to the pelvic flexure in the left ventral colon or orad to the transverse colon in the right dorsal colon; both are sites of colon narrowing. Large colon impactions are one of the most common causes of colic in horses. Impactions were responsible for 9% of colic cases in a farm population, second only to simple medical colic (83%). The disease accounted for 7.4% of all colic diagnoses in a study of university referral centers.

Traditionally, impactions are thought to be caused by overfeeding, especially of bulky feed containing an excess of indigestible residue; old, dry, hard hay, or stalks; deficiency of secretions in the intestinal tract; lack of water, want of exercise, medicines, etc. These same associations are commonly reported to this day. Poor teeth, lack of water, particularly in cold climates when drinking water freezes, alterations in exercise or housing, parasites, and nerve damage have all been related to large colon impactions but remain anecdotal associations.

Specific risk factors have not been identified by epidemiologic studies, but case reports identify poor teeth, decreased water intake, and diets with a high percentage of indigestible fiber or fibrous material as the most highly associated risk factors. Acute alterations in activity, such as stall confinement after surgery or injury, are also suspected to increase the risk of large colon impaction. Researchers have speculated that reduced exercise may affect colonic motility and cause impaction, although a change in diet or new bedding are also factors that may increase the risk of colon impaction. Administration of non-steroidal antiinflammatory drugs (NSAIDs) has also been found to decrease colonic muscle contractility *in vitro*. Although use of these drugs has not been proven as a cause of colon impaction in live horses, administration of phenylbutazone may be a risk for cecal impaction. Infection with small strongyles hypothetically irritates the colonic wall and causes alterations in colon motility. Although controlling infestation with small strongyles has been shown to decrease the incidence of colic, this is not a specific risk factor for large colon impaction.

Exposure to Amitraz, a formamidine acaricide with  $\alpha_2$ -adrenergic activity, can cause large colon impaction. Colon impactions have also been reported in horses with colon adhesions caused by pelvic flexure fistulas. However, the majority of clinical cases have no identifiable cause.

Horses with large colon impactions that require extensive medical treatment or surgery have a high recurrence of colic, which suggests that these horses are at increased risk or that the impaction is severe enough to cause permanent changes in colon function or motility. In cases of large colon obstruction that persists for more than 24 hours, neurons in the myenteric plexus are significantly decreased compared with normal horses or those with acute obstruction. Whether neuron loss is a precondition or a sequela to the obstruction is unknown, but the finding suggests that alterations in the nerve function may play a role in some cases of colon obstruction similar to that seen in cecal impaction associated with cecal hypertrophy.

The large colon serves as a third space reservoir of water for the horse, and systemic dehydration can cause dehydration of the colonic content. This reserve is decreased by as much as one-half in horses fed only a concentrated diet. A state of transient dehydration has been produced experimentally in horses fed meals of large grain. When grain is fed as a single bolus, rapid production of volatile fatty acids in the colon causes movement of water from the extracellular space to the colon lumen. This response causes an increase in aldosterone because of transient systemic dehydration. Subsequent fluid absorption with the volatile fatty acids hypothetically causes a relative dehydration of the colon contents. This cyclic shift of water subsequent to feeding high-concentrate diets does not occur in horses fed grain every 2 hours. On the basis of this experimental work, researchers have hypothesized that feeding grain once or twice daily could create the initial conditions for a colon impaction. However, this hypothesis has not been supported by published case reports or epidemiologic studies.

Initial results from experiments that changed a horse's diet from an *ad libitum* hay-only diet to a diet of *ad libitum* hay with grain fed at 12-hour intervals suggest that the latter diet produces an increased dry matter content in the right dorsal colon. The higher dry matter content is maintained as the diet is continued. Although not specific for colon impaction, grain fed in large amounts daily increases the risk of colic.

Simple dehydration of large colon ingesta observed in horses with small intestinal disease and systemic dehydration in clinical cases does not result in colon obstruction. The dehydrated ingesta from systemic dehydration rarely distends the colon, suggesting that transient dehydration alone does not cause large colon impaction.

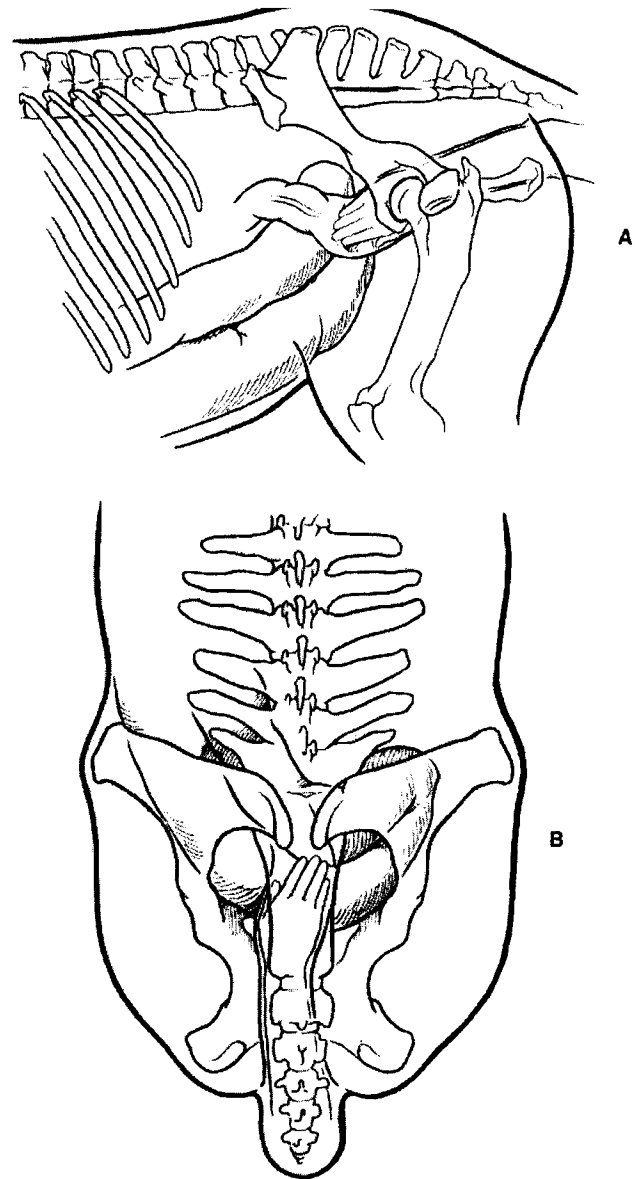
## CLINICAL SIGNS

Pain from impaction colic usually is mild, intermittent, and slow in onset. Initially some horses are depressed before colic is observed. Horses display colic by pawing, frequent periods of recumbency, turning the head to the flank and frequently standing in a stretched-out posture as if to urinate. None of these signs is specific for colon impaction, although stretching has been suggested to be more common with this type of obstruction. Pain may intensify during progressive peristalsis and possibly may be associated with auscultation of borborygmi. Decreased fecal production consisting of dry fecal material is frequently a precursor to signs of obstruction. The body temperature is usually normal. Pulse rate may be normal or have a mild increase (40-50 bpm) depending on the degree of dehydration and pain. Horses with higher heart rates often have massive bowel distention and/or signs of shock. Similarly, the respiratory rate is frequently increased parallel to the intensity of colic. Most horses with colon impaction have normal mucous membrane color and refill time. If the impaction is chronic, dehydration causes prolonged mucous membrane refill time, but this is rare. If the colon circulation is compromised by distention, signs of shock and endotoxemia can occur.

Large colon impaction rarely causes gastric reflux. If the impaction is complicated by a displacement, gastric reflux is more likely, as the duodenum can be obstructed at the base of the colon mesentery. Palpation per rectum is important to make the diagnosis of a large colon impaction. If the pelvic flexure is affected, it will be distended and located just in front of the pelvic brim or just to the right of the pelvic canal. The clinician may mistake this position for right displacement of the large colon, but often the distended ventral colon can be felt coursing from the right dorsal to the left ventral abdomen (Figure 3.14-1). The pelvic flexure and left ventral colon will be distended and create a smooth surface that obliterates the normal saclike haustra. The material in the pelvic flexure is usually firm but normally can be indented with the hand pressing on the colon. When the colon undergoes acute dehydration secondary to systemic dehydration or shock, the colon is in normal position and though the ingesta is firm, the colon shape is not distorted and the haustra are maintained. If an impaction of the transverse or right dorsal colon is present, the clinician may not be able to reach the impaction by rectal palpation.

Tympany of the colon and/or cecum may accompany an impaction. Frequently the tympany caused by impactions cannot be distinguished from other colon obstructions and may resemble the distention found with colon displacement. Because of the gas distention, the colon can move into abnormal positions within the abdomen. Although it is not normally felt per rectum, the right dorsal colon is frequently involved at the same time as the pelvic flexure impaction and can cause dorsal colon tympany. Colon distention may prevent palpation of the impaction and make the definitive diagnosis difficult.

The clinician should obtain peritoneal fluid by paracentesis if evidence exists of shock, ileus, or abdominal distention. If the colon is markedly distended with a large impaction, an increased risk exists of penetrating the colon during paracentesis because it is heavy and often



**Figure 3.14-1** **A**, Left lateral view of a rectal examination for a large colon impaction. The pelvic flexure is pushed back to or over the pelvic brim, and the colon is enlarged, losing the definition of the haustra on its surface. The ingesta is usually firm but can be indented during palpation. **B**, A dorsal view of the rectal examination for a large colon impaction. The pelvic flexure is frequently located on the right side of the pelvis and characteristically enters the pelvis from the right side.

positioned near the ventral midline. Ultrasound may be helpful to identify the colon and pockets of peritoneal fluid, which can be aspirated by paracentesis. Because impactions are simple obstructions, peritoneal fluid is usually normal. However, the total protein increases slowly as time or the amount of distention increases. Red blood cells are rarely seen except in cases of marked distention when the bowel wall becomes ischemic and edematous.

Ultrasound may be useful to visualize the obstructed segment. The impaction appears as an intraluminal hyperechoic mass. If any gas is present in the colon, a hy-

perechoic interface that blocks ultrasound penetration will occur at the colon lumen. The primary benefit of ultrasound is to identify colon distention, an edematous colon wall, or sand within the colon.

Determining the need for surgery in cases of large colon impaction is similar to the decision-making process for any horse with colic. Horses that have ileus, unrelenting pain, excessive colon distention, lack of response to analgesics, or progressive change in the peritoneal fluid that suggests bowel injury are candidates for surgery. Horses that need surgery usually have higher heart rates consistent with moderate-to-severe pain or dehydration. In some cases the size of the impaction as determined by rectal examination suggests surgery will be necessary, but this is not a consistent finding because very large impactions can respond to medical therapy. Furthermore, surgery may be necessary to treat another intestinal problem that occurs with a large colon impaction. The most consistent surgical indicator in these authors' experience is the lack of response to analgesic administration, which would normally relieve pain caused by an impaction.

## TREATMENT

The primary goal in treating large colon impaction is to restore intestinal transit of ingesta, which usually requires administration of analgesics and cathartics to facilitate evacuation of impacted ingesta. One key to successful treatment is to curtail all oral intake of feed. Horses fed concomitantly with laxative treatment and analgesia can experience repeated colic and/or no change in the size or consistency of the impaction. Horses with large impactions can make a full recovery even when held off feed for as long as 6 days.

Administration of analgesics is essential to preserve gastrointestinal (GI) motility. However, the smallest dose that resolves pain should be used so as not to mask signs of a serious disease or the need for surgery. Analgesia with flunixin meglumine is efficacious alone or combined with  $\alpha_2$ -adrenergic agonists such as xylazine or detomidine. Flunixin by itself may be effective at a dose from 0.25 to 0.5 mg/kg administered intravenously every 6 hours. When the 0.5-mg/kg dose is not sufficient to relieve pain, increasing the dose to 1 mg/kg may be successful, although this dose may suppress the pain that signals the need for surgery. If pain is observed within an hour after flunixin administration or after repeated flunixin administration, surgical exploration should be considered to either empty the colon or diagnose another concurrent intestinal problem.

Xylazine and detomidine are both potent analgesics that provide sedation and colon relaxation. Xylazine administered by titration at 0.2 to 0.4 mg/kg intravenously as needed is usually sufficient to relieve the pain from colon spasms. At 0.5 to 2.0 mg/kg injected intramuscularly, xylazine can provide longer analgesia. Titration with detomidine is also an effective analgesic, even though it is much more potent than xylazine. Typically, 10 to 20  $\mu$ g/kg intravenously is sufficient to control pain. When combined with flunixin meglumine, xylazine or detomidine often provide immediate relief, and further treatment with either of the latter drugs is usually not needed. If

pain returns within 30 minutes after xylazine or 60 minutes after detomidine administration, reevaluation is indicated and surgery may be necessary.

The combination of a dipyrone and a scopolamine derivative found in Buscopan has been used successfully in Europe and South America to treat impaction of the colon. Similar to the  $\alpha_2$ -adrenergic agonists, this combination decreases intestinal contraction, thereby decreasing pain. Butorphanol also causes cessation of colon motility and may help relieve pain from an impaction. Butorphanol, which has a short duration of action, is not as efficacious, and may cause excitement if used alone.

Mineral oil is traditionally used as a lubricant to help relieve the impaction. The dose is usually 4 to 8 ml/kg. Mineral oil can pass over a dense impaction and appear at the anus without relieving the obstruction. Its use with analgesia may be sufficient; mineral oil appears to soften feces in mild impactions, although its efficacy has never been scientifically proven. Large or firm impactions frequently do resolve with administration of one or more doses of mineral oil. If an impaction does not respond to one dose of mineral oil, hydration of the impaction should be attempted to initiate transit.

Oral administration of ionic cathartics and fluid to hydrate and soften the impaction is an effective treatment for large colon impaction. Intravenous (IV) administration of lactated or acetated Ringer's solution also appears to be an effective treatment when combined with analgesics and restriction of oral intake of feed. The goal of IV fluid administration is to increase plasma volume and decrease the osmotic pressure of the plasma, thereby allowing fluid to move into the extracellular space with subsequent secretion into the bowel lumen. The patient usually tolerates fluid administration at two to three times maintenance, with rates of as much as 5 L per hour. IV administration of fluids with or without laxatives has reportedly been effective in the resolution of large colon impaction. The average time for resolution of resistant impactions treated with IV overhydration is approximately 2 days, with total fluid volumes ranging from 54 to 350 L per treatment. During administration the total plasma protein should be monitored to ensure that the concentration is decreased. If fluid administration is necessary for more than 24 hours, electrolytes should be monitored to ensure that no deficit of plasma potassium or calcium exists. Serum magnesium also should be checked in horses that are not fed for 3 or more days. Unless ileus is present, horses are allowed free choice water during IV fluid therapy.

Although few complications result from the administration of large volumes of fluids for several days, thrombophlebitis is the most frequent problem. Catheter maintenance is critical, and the catheter should be monitored each time the fluid source is changed. Catheters should be changed whenever signs of vein inflammation or thrombus formation are noted or after 48 to 72 hours if the catheter is made from a reactive material such as polyethylene.

Magnesium sulfate, an ionic cathartic, is administered at 1 g/kg through a nasogastric tube once daily for as many as 3 days. Administration has been shown to increase fecal water within 3 hours of administration, suggesting that its action is mediated at least in part by reflex secretion in the large or small colon. Magnesium toxicity

is rare at the recommended dosage but possible with continued administration. Recent studies suggest that sodium sulfate (1 g/kg PO) is more efficient than magnesium sulfate in increasing water in the ingesta and feces but that administration can result in hypernatremia, hyperchloremia, and hypocalcemia. Therefore a lower dose (0.5 g/kg PO) and monitoring serum electrolytes if administration is repeated are recommended. Both treatments are effective in increasing water content in the colon and as initial treatments for colon impactions.

Administration of large volumes of water through a nasogastric tube (as much as 10 L q30min) has been used successfully to treat colon impaction. The average time for resolution of an impaction after initiation of enteral water administration through a stomach tube is 2½ days, with water volume ranging from 85 to 208 L. Water can be administered by a nasogastric feeding tube connected to a fluid reservoir so that the dose can be delivered accurately over time. Water should not be administered without monitoring of plasma electrolytes because it can cause severe hyponatremia. Enteral administration of large volumes of saline is not recommended because both hypernatremia and hyperchloremia occur during the treatment. Use of a balanced electrolyte solution with electrolyte concentrations comparable to plasma may prevent changes in plasma electrolytes. Frequent monitoring of plasma electrolytes should be used to determine when changes in electrolyte composition are necessary.

The rate of enteral fluid administration and the systemic response must be monitored. Before enteral fluid administration is initiated, the stomach should be checked for gastric reflux. Abnormal GI transit evidenced by gastric reflux is a contraindication for enteral fluid therapy. Although rare, ileus may be present during large colon impaction. The frequent administration of enteral fluid can easily overload the GI tract when it has lost progressive motility. Monitoring for increased heart rate, respiratory rate, and pain during the treatment is necessary for early recognition of excessive gastric distention. If ileus or gastric distention is detected during enteral fluid therapy, administration should be stopped until evidence of gastric emptying is noted.

Although loose or watery feces may be observed during the treatment, the success of the therapy should be based on clearance of the impaction as confirmed by rectal examination. Once the impaction is no longer palpable, fecal production has returned to normal, and the horse exhibits normal vital signs—including intestinal sounds—fluid therapy ceases. Analgesic therapy should also be stopped or decreased once intestinal transit has been reestablished. If the impaction caused a long period of distention, treatment with flunixin meglumine is frequently continued until the horse can tolerate a free choice diet. Hypothetically, this treatment helps resolve mural inflammation resulting from the distention.

IV and enteral fluid therapy may be combined, particularly when IV fluid administration is necessary to correct severe systemic dehydration while enteral fluid therapy is initiated. However, dehydration is usually not severe in horses with large colon impaction, and enteral fluid therapy alone may be sufficient to correct systemic dehydration.

Diarrhea may occur after enteral or IV overhydration

and after administration of salts, such as  $\text{MgSO}_4$  or  $\text{Na}_2\text{SO}_4$ , particularly after repeated doses. Diarrhea is expected in some cases after enteral treatment and is a sign that the impaction has been adequately hydrated. However, diarrhea may also be the result of colitis concurrent with or subsequent to the impaction. Horses with excessive diarrhea and systemic signs of shock, fever, and depression should be evaluated for infectious enteritis.

After evacuation of the impaction, feed is reintroduced during a 48-hour period. Hay or grass is provided in small amounts (0.25–0.5 kg q3h). This interval allows the stomach to empty and does not overload the cecum or colon but is usually only necessary for 12 to 24 hours, after which hay or grass may be fed ad libitum. The rate of return to full feed is determined through monitoring of the horse for signs of colic, fecal transit, and vital signs. If colic is observed, feeding should be stopped until confirmation is obtained that the original problem has not recurred or that no other abdominal problems are present. Grain should not be introduced into the diet until the horse has established normal transit on a hay or grass diet. Introduction should be gradual during a 4- to 7-day period.

Surgery is necessary for very large impactions that cause ileus or extreme colon distention with mural ischemia or to treat pain that cannot be controlled. Although the technique for large colon enterotomy is straightforward, the risk of rupture makes the removal of the colon from the abdomen the most critical part of the procedure. Because the colon wall is often thin and friable from distention, inadvertent use of the fingers to grasp or pull the colon can easily result in rupture. When the clinician encounters a massive impaction, the abdominal incision should be enlarged to allow entry of both arms to encircle the colon. The clinician moves the colon by a gentle rocking to slowly bring the pelvic flexure out of the abdomen. In some cases the enterotomy should be completed before the entire colon is removed from the abdomen so as not to increase the risk of rupture with repeated lifting and manipulation.

## PROGNOSIS

The prognosis for horses with large colon impaction is good, with a greater-than-90% survival rate. Cases that require surgery have a lesser chance for survival because of the risk of rupture during surgery and because of damaged intestine or progressive shock in severe cases. Heart rate, peritoneal fluid protein concentration, and plasma lactate concentration are significantly higher in nonsurvivors, whereas systemic leukocyte numbers are significantly lower compared with survivors. However, these values have not been used to predict survival with large colon impactions.

In one group of 25 horses discharged after treatment for resistant impactions, 30% had one or more colic episodes after dismissal from the hospital. This number is in agreement with reports that found that for horses with a history of colic, the risk for future episodes of colic is increased by as much as 3 times. Because horses with chronic colon obstruction (>24 hours) reportedly have a decrease in the number of myenteric neurons, recurrent colic may be related to motility dysfunction. Therefore



horses with a history of prolonged obstruction of the colon should be considered at higher risk for future episodes of colic.

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White NA, Dabareiner RM: Treatment of impaction colics. *Vet Clin North Am Equine Pract* 1997; 13:243-259.

## CHAPTER 3.15

# Large Colon Volvulus and Reperfusion Injury

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**A**cute gastrointestinal (GI) tract disease (colic) is the leading natural cause of death in adult horses. GI tract ischemia commonly develops secondary to low-flow/no-flow conditions; small intestinal volvulus or incarceration and large colon volvulus are common causes. Strangulating obstructive lesions are associated with the highest mortality rates (75%) of all types of colic, and large colon abnormalities account for as many as 50% of the horses that die or are euthanized because of colic.

Strangulating volvulus of the ascending colon in horses has been reported to have a mortality rate that approaches 80%. The disease is characterized by colonic luminal obstruction and vascular occlusion secondary to the volvulus that results in colonic ischemia, mucosal necrosis, and vascular thrombosis. Ischemia and subsequent reperfusion results in tissue edema, inflammatory cell influx, increased cell membrane and microvascular permeability, and hemorrhage and necrosis of the intestinal wall. The majority of injury occurs in the mucosal epithelium because it is the most metabolically active layer.

After ascending colon volvulus is experimentally induced, colonic blood flow remains significantly below baseline values for at least 4 hours after correction of complete arteriovenous occlusion. The high mortality associated with colonic volvulus may be related to a sustained reduction of blood flow and hypoperfusion (caused by increased vascular resistance) after surgical correction and continued ischemic injury. Endothelial damage occurs in the colonic vasculature subsequent to ischemia-reperfusion injury and can be exacerbated by endotoxins. The sustained decrease in colonic blood flow may be associated with endothelial damage in the colonic circulation that leads to a loss of endothelium-derived vasorelaxants

and subsequent vasoconstriction. Many of these horses develop systemic hypotension as a result of hypovolemia and endotoxemia, which contribute to decreased splanchnic blood flow. Additionally, colonic mucosal adenosine triphosphate (ATP) content has been shown to decrease 92% during ischemia and recovers to only 44% of control value after reperfusion, thereby limiting substrate availability for cellular metabolic functions. Ultimately, colonic ischemia leads to disruption of the mucosal barrier and transmural passage of endotoxin into the splanchnic circulation. If sufficient endotoxin enters the systemic circulation, death can ensue.

### REPERFUSION INJURY

Most tissues in the body (including the GI tract) have significant energy reserves and the capability to increase oxygen extraction. Within the mitochondria, oxygen is reduced and ATP is synthesized. During ischemia, anaerobic glycolysis produces ATP inefficiently, and increased production of lactic acid and hydrogen ions occurs, leading to intracellular acidosis and further inhibition of ATP synthesis. Insufficient ATP and energy are available to run membrane pumps; cellular ionic balance cannot be maintained; and accumulation of intracellular calcium leads to cellular swelling. Alterations in membrane permeability result in enzyme leakage into the extracellular environment. Irreversible changes occur within the cells, which eventually die.

On reintroduction of oxygen during reperfusion, reactive oxygen species are produced when oxygen reacts with xanthine oxidase and the accumulated hypoxanthine to produce superoxide anion. In horses the xanthine dehydrogenase and

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On reintroduction of oxygen during reperfusion, reactive oxygen species are produced when oxygen reacts with xanthine oxidase and the accumulated hypoxanthine to produce superoxide anion. In horses the xanthine dehydrogenase and

xanthine oxidase enzyme system is present in the small intestine. However, in the mucosa of the large bowel, activity of these enzymes is low. Additional sources of superoxide anion may include components of the electron transport chain, certain flavoproteins, hemoproteins, amine oxidases, aldehyde oxidase, and reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. In aqueous environments, superoxide anion is relatively unstable and dismutates to hydrogen peroxide and oxygen. Superoxide anion acts as both an oxidant and a reductant. As a weak oxidant, it can inactivate specific enzymes essential to cellular function. It is not highly toxic but can generate other highly toxic radicals, such as hydroxyl radical, an extremely powerful oxidant.

Hydrogen peroxide, formed by divalent reduction of oxygen or dismutation of superoxide anion by superoxide dismutase, is a powerful but slow oxidant and is the precursor of hydroxyl radicals. Hydrogen peroxide can readily diffuse across cell membranes and react with transition metals to form hydroxyl radical. It can cause lipid peroxidation of cell membranes, depolymerize hyaluronic acid, degrade collagen, inactivate enzymes and transport proteins, and cause mutagenesis by damaging DNA.

Reactive oxygen metabolites have numerous biologic activities, ranging from direct cytotoxicity toward endothelial and epithelial cells to nontoxic alterations in intestinal function. For example, hydrogen peroxide can increase expression of P-selectin, which enhances neutrophil adhesion to endothelial cells. Reactive oxygen metabolites can also enhance platelet aggregation.

Lipoperoxidation of cell membranes by reactive oxygen metabolites leads to structural and functional alterations and the generation of many phospholipid-derived inflammatory mediators. For example, leukotriene B<sub>4</sub> and platelet-activating factor are phospholipid-derived mediators that are potent chemoattractants for neutrophils. Lipoperoxidation after experimentally induced low-flow arterial ischemia in the equine ascending colon has been documented.

Neutrophils play an important role in ischemia-reperfusion injury, accumulating in the mucosa of the large colon subsequent to experimental low-flow ischemia and reperfusion. Neutrophil accumulation develops in submucosal venules of the large colon and peaks during the early period of reperfusion. The increased microvascular permeability observed in the ascending colon after ischemia-reperfusion may be subsequent to adhesion and diapedesis of inflammatory cells through the vascular endothelium. When neutrophils are activated, the respiratory burst leads to generation of more oxygen radicals that compound the cellular injury. Activated neutrophils also release lysosomal granules composed of elastase, gelatinase, and collagenase that break down the interstitial matrix and capillary basement membrane.

Numerous inflammatory mediators are involved in ischemia-reperfusion injury. For example, platelet-activating factor—which is formed by endothelial cells, neutrophils, macrophages, and platelets—can cause platelet aggregation and degranulation, smooth muscle contraction, neutrophil activation and chemotaxis, and increased vascular permeability. Arachidonic acid metabolites, leukotriene B<sub>4</sub>, and thromboxane A<sub>2</sub> have been implicated

as mediators of neutrophil recruitment and microvascular dysfunction.

Controversy exists regarding reperfusion injury in the large colon of horses after experimentally induced ascending colon volvulus. Several *in vivo* models of hemorrhagic and ischemic strangulation obstruction have failed to document evidence of reperfusion injury, whereas others have demonstrated histologic changes compatible with reperfusion injury in the mucosa of the large colon after low-flow arterial ischemia. However, reperfusion injury was not attenuated when horses were treated with dimethyl sulfoxide (DMSO), a scavenger of free radicals, or allopurinol, a competitive inhibitor of xanthine oxidase. The contradictory results between studies of reperfusion injury in horses is likely a reflection of the models of ischemia and reperfusion used and the variables used to assess development of cellular injury. However, evidence exists to suggest that reperfusion can exacerbate large colon injury after ischemia.

## ASCENDING COLON VOLVULUS

Ascending colon volvulus affects all breeds and ages of horses. However, adult horses are more commonly affected, and mares are at greater risk than geldings and stallions. Late-gestation and early-postpartum mares are at greatest risk of developing a volvulus of the large colon. Several theories have been proposed, including increased mobility of the colon after parturition; repositioning and partial obstruction of the ascending colon because of the presence of the late-gestation uterus; and dietary changes resulting in a higher carbohydrate to fiber ratio, increased fermentation, and subsequent decreases in intestinal motility.

Development of the volvulus usually occurs at the level of the cecocolic ligament, but volvulus at the base of the cecum or at the sternal and diaphragmatic flexures can also occur. A 360-degree volvulus is the most common finding, but rotation of as much as 720 degrees may occur. The most common form of ascending colon volvulus is hemorrhagic strangulation obstruction in which a disparity exists between arterial and venous flow. However, occasionally complete arteriovenous obstruction occurs, producing ischemic strangulation obstruction. After 3 to 4 hours of complete arterial and venous occlusion, irreversible damage to the colonic mucosa occurs.

During hemorrhagic or ischemic strangulation obstruction, sequestration of fluid in the subepithelial space occurs and causes the epithelium to loosen from the basement membrane. Cellular necrosis leads to sloughing of clusters of cells. If the animal survives the initial period of mucosal necrosis and sloughing and if viable enterocytes are present, the mucosa can regenerate. The mucosa will be covered by epithelium within 12 to 24 hours after the injury.

Clinical signs usually reflect the duration and degree of the volvulus. The severity of the pain is directly related to the degree of the volvulus, tension on the mesocolon, and the amount of secondary gas distention. Affected horses usually respond poorly to routine analgesics. Sweating, tachycardia, tachypnea, and gross abdominal distention are common clinical findings. Examination of oral mu-

cous membranes initially reveals either normal or pale membranes that rapidly progress to a purple color with poor capillary refill time. Hematologic and serum biochemical values frequently reflect the degree of dehydration, endotoxemia, and GI protein loss that is present. Palpation per rectum reveals a markedly gas-distended colon and tight bands of tenia. Mural and mesocolic edema are sometimes palpable. Results of peritoneal fluid analysis are variable and depend on the degree of intestinal wall damage that has occurred.

## Treatment

Because of the rapid deterioration of the colon, early diagnosis and surgical intervention constitute the only treatments available for ascending colon volvulus. Many horses present with poor cardiovascular status secondary to severe dehydration and endotoxemia. Aggressive fluid therapy with crystalloids to expand the intravascular space and maintain venous return and cardiac output is imperative. Broad-spectrum antimicrobial agents and flunixin meglumine should be administered before surgical intervention. Before the colon is untwisted, colloids and endotoxin antibodies should be administered to help attenuate the effects associated with the sudden release of endotoxin that occurs as the colon is reperused.

After relief of the torsion, the viability of the ascending colon must be assessed to help determine whether a colon resection should be performed or whether intraoperative euthanasia is warranted. Methods to assess intestinal viability include visual and tactile assessment, fluorescein uptake, Doppler flow, surface oximetry, intraluminal pressure, and histology. Clinical appearance (e.g., color, motility, bleeding from an enterotomy site) is subjective and can be affected by mean arterial blood pressure and anesthetic agents. The clinician can evaluate blood flow by using Doppler ultrasound, laser Doppler, and fluorescein dye. Blood pressure, heart rate, intravenous (IV) fluid volume, and motion artifacts affect the results obtained with Doppler ultrasound and laser Doppler techniques. Fluorescein dye is injected IV (11 mg/kg of 25% solution), and the presence of dye in the injured bowel is evaluated after 3 minutes. The same factors affect the results obtained with fluorescein dye that affect other blood flow assessment techniques.

Assessment of oxygen tension with surface oximetry is objective but depends on diffusion distance from the nearest vessels, oxygen content of the blood, and regional blood flow. The prognosis is good if oxygen tension is greater than 20 mm Hg. In a study that evaluated colonic luminal pressure as a predictor of survival, luminal pressure was greater in nonsurvivors than in survivors. Luminal pressure values greater than 38 cm H<sub>2</sub>O were relatively sensitive and specific in predicting death. However, none of these techniques can assess the degree of cellular injury. The only method to directly assess cellular injury is histomorphologic evaluation of frozen sections. This technique is objective and accurate. If the interstitial:crypt (I:C) ratio is 1:1, glandular loss is less than 25%, and minimal edema/hemorrhage are present, the prognosis is good. If

the I:C ratio is greater than 1 but less than 3, glandular loss is between 25% and 50%, and edema/hemorrhage is moderate, the prognosis is guarded. A poor prognosis is warranted if the I:C ratio is greater than 3, there is greater than 50% glandular and greater than 97% surface epithelium loss, and severe edema/hemorrhage is present. In a recent study that used pelvic flexure biopsies to predict survival after ascending colon volvulus, morphologic variables correctly predicted survival or death in 51 of 54 horses.

During the immediate postoperative period, endotoxemia and ischemia-reperfusion injury can continue. If the colon is viable, heart rate will increase; mucous membrane color and capillary refill time will improve, GI motility will increase, and hematologic values will normalize. If the heart rate does not stabilize or increases during the first 24 hours postoperatively, the prognosis for survival is guarded or poor.

## Prognosis

Reported survival rates range from 12% to 35%, but approximately 50% of horses are euthanized during surgery because of the severity of the lesion. The prognosis is largely influenced by the severity and duration of the vascular compromise to the ascending colon. Early recognition of the disease and surgical intervention improve outcome. When resection is performed, survival is related to the length of intestine resected. Many horses die or are euthanized in the early postoperative period because of endotoxemia and continued deterioration of the colon. If the colon has been significantly compromised, subtotal colonic resection should be attempted. The resection should be performed as close to the cecocolic ligament as possible. However, the severe mural and mesocolic edema makes exteriorization and successful resection difficult or impossible.

After colon resection at the level of the cecocolic ligament, digestion of crude protein, cellulose, and phosphorus is markedly decreased. Because of the reduction in intestinal length, the transit time of the digesta is shorter. Fecal water and total fecal outputs are increased. In the initial postoperative period, most horses lose weight; however, by 6 months after the surgery, most horses can compensate for the loss of colon length.

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## CHAPTER 3.16

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# Cecal Impaction

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As a cause of colic in horses, cecal impaction is an infrequent finding that accounts for approximately 2% to 5% of colic cases in a referral hospital population. However, cecal impaction is the most commonly diagnosed form of cecal disease and because of its obscure and often insidious onset, it can pose a challenging clinical problem. In addition, the exact etiology and pathogenesis of cecal impaction are currently unknown; therefore the appropriate management of the condition continues to be controversial.

### ANATOMY AND PHYSIOLOGY

The cecum lies along the right abdominal wall, extending from dorsal to ventral as a comma-shaped viscus approximately 1 m long. Dorsally, the cecal base has extensive retroperitoneal attachments and fuses with the mesenteric root medially and the right dorsal colon cranially. The cecal base is divided into a cranial, overhanging pouch (the cupula), and a caudal compartment. The body of the cecum interposes between the base and the ventrally located, blind-ended apex. The average capacity of the cecum is 33 L. The viscus is demarcated by horizontal haustra and four longitudinal teniae. The well-developed medial and lateral teniae are joined by the smaller dorsal and ventral teniae, respectively, before they coalesce at the cecal apex. The ventral tenia is usually palpable per rectum as a band of tissue coursing in a cranioventral and medial direction. The lateral tenia is attached to the right ventral colon by the cecocolic ligament and the dorsal tenia continues as the ileocecal fold onto the ileum.

The ileocolic artery, a branch of the cranial mesenteric artery, gives rise to the lateral and medial cecal arteries that course toward the cecal apex in the lateral and medial cecal tenia, respectively. The lateral and medial cecal arteries have minimal collateral communication; however, each artery furnishes a mesh-like network of vessels called the cecal rete. This vascular arrangement likely provides an alternative route for blood supply should an artery thrombose.

The cecum performs an important, but not vital, digestive function in the horse. It is a site of water and electrolyte absorption, and microbial digestion of soluble and insoluble carbohydrates. The cecocolic orifice is dorsal to the ileocecal orifice and lies in the caudal wall of the cranial base. The normal functioning of the cecocolic orifice may be interfered with when excessive distention (with gas or digesta) of the cranial cecal base causes it to compress the orifice and origin of the right ventral colon.

Motility patterns have been identified that mix, retain, and propel cecal contents. Three intracecal patterns involve contractions that move from cecal apex to cranial base, cranial base to cecal apex, and cecal apex to caudal base. These haustra contractions occur every 20 to 30 seconds and account for the gurgling and tinkling sounds heard on auscultation of the right dorsal abdominal quadrant. A fourth major contraction begins in the cecal body/apex and progresses aborally through the cecal base, the cecocolic orifice, and into the right ventral colon, serving to propel cecal contents further along the large intestine. This contraction occurs about once every 2 to 4 minutes and is responsible for the distinct, loud "flushing" sounds heard on auscultation. An electrical pacemaker is believed to exist in the region of the cecal apex that is critical to normal functional motility.

### PATHOGENESIS

Cecal impactions have been categorized on the basis of their apparent occurrence as primary or secondary events or, alternatively, on the consistency of the obstructing digesta. The varying classification descriptions in the literature are a reflection of the unknown pathogenesis of cecal impaction. Previous authors have proposed a disruption to the normal cecal outflow mechanism, caused by either an abnormality in progressive cecal motility or by retro-pulsive activity in the right ventral colon that causes cecal digesta accumulation. Evidence of mechanical obstruction at the cecocolic orifice is rare in horses in North America. In Europe, chronic, recurrent cecal impaction has been described in the horse that is associated with hypertrophy of the muscle layers of the cecum and a reduced neuronal density in the myenteric plexus of the cecal base. It is hypothesized that a retention of digesta in the cecal base leads to partial or complete closure of the cecocolic orifice. Subsequent cecal contractile activity that attempts to propel digesta aborally results in hypertrophy of the smooth muscle. The frequent contractile state could reduce blood flow to the cecal wall and therefore adversely affect the neuron density.

Few proven risk factors for cecal impaction exist, but adult horses are more likely to present with the condition than immature animals. In one report, Arabian, Morgan, and Appaloosa breeds were overrepresented among horses with cecal impaction. Infection with the tapeworm *Anoplocephala perfoliata* has been incriminated in cases of cecal impaction, but a direct causal relationship has not been established.

Primary cecal impaction is thought to be associated

with ingestion of coarse roughage diets, diets high in corn cobs or kernel corn, abrupt dietary changes, reduced exercise, poor dentition, and reduced water intake. This condition can also occur for unknown reasons in horses on normal diets. Secondary cecal impaction is recognized in horses that are being treated for unrelated illnesses, including orthopedic, upper respiratory, and other gastrointestinal (GI) conditions. This population of hospitalized horses has often undergone general anesthesia and received nonsteroidal antiinflammatory drugs (NSAIDs) perioperatively. It has been suggested that fasting, surgery, general anesthesia, and perioperative medications, including antibiotics and analgesics, may have an adverse effect on cecal motility. Progressive cecal motility is decreased by fasting but returns after feed intake resumes. Intestinal myoelectric activity is significantly depressed by general anesthesia regardless of the anesthetic regimen. For general anesthesia periods lasting less than 1 hour, myoelectric activity can be depressed for as long as 3 hours after induction. The  $\alpha_2$ -adrenergic agonists (e.g., xylazine) inhibit acetylcholine release from cholinergic neurons in the enteric nervous system and therefore suppress intestinal contractions. Intravenous (IV) xylazine reduces cecal and colonic myoelectric activity in a dose-dependent fashion for as long as 90 minutes, but its effects on cecal emptying after a single dose are short-lived. The addition of the partial opiate agonist, butorphanol, prolongs the depressive effects of xylazine on cecal myoelectric activity. The NSAID flunixin meglumine appears to have little effect on cecal motility and emptying in normal horses.

When classified according to the consistency of the digesta, cecal impactions are divided into those that appear to be dehydrated with firm digesta and those that have a softer, more fluid content. Primary cecal impactions are typically made of firm, dry contents whereas the more fluid impactions are generally found in horses with secondary cecal impaction. The horse with a tightly distended cecum containing loose contents has also been described as having cecal dysfunction. This condition implies a cecal motility disorder; a lack of aboral movement of digesta from the cecum could explain why the right ventral colon is commonly found to be devoid of intestinal contents in horses with cecal dysfunction.

## CLINICAL SIGNS AND DIAGNOSIS

Clinical signs tend to vary with the type of cecal impaction, however, differentiation of primary and secondary impaction may be very difficult. Horses with a firm, dehydrated mass of digesta frequently exhibit mild to moderate, intermittent abdominal pain that may develop during the course of several days. These horses usually have a mildly elevated heart rate, reduced borborygmi, decreased and semiformed fecal output, and inappetence. A cecal gas cap may be percussed in the right dorsal abdominal quadrant. On palpation per rectum, a distended cecum containing a firm, dry mass of digesta can be identified. The mass may be slightly indented by finger pressure. The ventral cecal tenia will be taut but the cecal wall should not feel thickened. Abdominocentesis generally reveals a normal peritoneal fluid.

Horses with secondary cecal impaction usually develop moderate to severe abdominal pain, with associated high heart rates, absence of borborygmi, and scant, loose feces. The cecum is more compromised in these patients, which may result in signs of systemic endotoxemia. On palpation per rectum a grossly distended cecum is identified that is filled with a fluid digesta. Palpable cecal teniae are extremely taut and the cecal wall can be thickened. As the disease progresses, the cecal wall becomes compromised. Early in the course of the disease peritoneal fluid can have a normal to elevated protein concentration, with a normal straw color. Later, serosanguineous fluid can be found with an elevated neutrophil and red blood cell count in addition to a high protein concentration.

Palpation per rectum provides the definitive diagnosis of cecal impaction. A large colon impaction must be distinguished from a cecal impaction. Anatomically, palpation of the cecum can be confirmed by its location more to the right of midline and the inability to pass a hand dorsal to an impacted mass because of the attachments of the cecal base to the dorsal body wall and mesenteric root. The dorsoventrally coursing ventral cecal tenia is also a useful palpable structure to help identify the cecum.

Early diagnosis of cecal impaction is dependent on recognition of risk factors in association with subtle changes in fecal output and fecal consistency, decreased appetite, and signs of abdominal pain. Vague signs can be overlooked, particularly when concurrent clinical conditions are being managed. Analgesic administration and expected degrees of postoperative depression in horses that have recently undergone surgery may mask clinical signs of a developing cecal impaction.

## TREATMENT

Considerable controversy continues on the topic of the most appropriate treatment for cecal impaction because of the lack of understanding of the pathogenesis. Therefore both medical and surgical treatments are advocated, according to the classification of cecal impaction. Regardless of the type of cecal impaction, lack of any treatment endangers the horse to developing fatal cecal rupture. This outcome is more likely in cases of secondary cecal impaction if immediate treatment is not pursued. However, primary cecal impactions that have a gradual onset of abdominal pain during the course of several days may also rupture before the clinician is alerted to the condition. Rather than treat on the basis of attempted classification, the patient should be treated on the merits of the clinico-pathologic findings and anamnesis.

### Medical Therapy

Horses that are most amenable to medical treatment are those in which the diagnosis has been made early and that have mild signs of colic and minimal signs of systemic deterioration. Conservative therapy for cecal impaction is similar to the medical treatment of other large intestine impactions. The principles of treatment include the management of abdominal pain, softening of the impacted mass through IV and/or oral fluid administration, and the

withholding of feed until the impaction is resolved and normal intestinal function returns.

Control of pain is usually achieved with flunixin meglumine (0.25-0.5 mg/kg IV 3-4 times daily or 1.1 mg/kg IV q12h) or a combination of xylazine (0.1-0.3 mg/kg IV) and butorphanol (0.01-0.04 mg/kg IV), as needed. The route of administration and extent of fluid therapy will be influenced by whether the horse is being treated in the field or in a hospital. As a minimal starting point, nasogastric administration of water—with or without laxatives, lubricants, or cathartics—is required. In addition, 6 to 8 L of water may be administered every 2 hours through a nasogastric tube; early cases of cecal impaction can resolve with this fluid therapy alone. Hospitalized horses are likely to receive IV polyionic fluids at greater than maintenance rates (3-5 L/hour for the first 12-24 hours) to induce intestinal secretion into the mass of digesta. The IV fluids can be supplemented with oral fluid therapy. Psyllium hydrophilic mucilloid (1.0 kg in 4-8 L of water q6-8h) has been recommended as a bulk laxative. A delay of 24 to 48 hours can be expected before defecation occurs when this treatment is used. Mineral oil (2-4 L per 500 kg) is often used as a laxative. A possible disadvantage of mineral oil is its inability to deeply penetrate dry digesta. Dioctyl sodium sulfosuccinate (DSS; 10-20 mg/kg diluted in 1-2 L of water) is an anionic surfactant that can penetrate dehydrated digesta and aid in its breakdown. It is recommended that DSS be administered orally only once every 2 days for a maximum of two treatments, because it may alter intestinal absorption of electrolytes and water. Saline cathartics, for example, magnesium sulfate (Epsom salts, 1 mg/kg in 4 L of water) and sodium sulfate (Glauber's salt) provide an additional method to mobilize an impacted mass. Magnesium sulfate can be administered once or twice daily for as long as 3 days without any adverse effects. The osmotic cathartics are appropriate for use in conjunction with IV or additional oral fluids because of the potential for large fluid losses.

Pharmacologic stimulation of cecal motility has been investigated. Cisapride, erythromycin, bethanechol, and neostigmine have been shown to induce cecal emptying in normal ponies, and neostigmine (0.0125-0.025 mg/kg, SQ, IM, or slowly IV) has been used in clinical cases of cecal impaction. Overall, motility stimulants are not routinely used because of the risk that cecal rupture will be potentiated.

Successful medical therapy is heralded by increased fecal output, a diminishment of abdominal pain, and resolution of the impaction as palpated per rectum. Once the impaction has been cleared the horse should be gradually reintroduced to its normal dietary intake during the course of 2 to 3 days. An easily digestible, low-residue diet should be considered. Attention to possible etiologic factors such as poor-quality diet, inadequate water supply, dental disorders, and tapeworm infestation are advised.

### Surgical Therapy

Horses with cecal impactions that present as surgical colic should undergo emergency exploratory celiotomy. Frequently, these horses have developed cecal impaction con-

current to the treatment of an unrelated condition. Alternatively, these horses may represent cases of primary cecal impaction that have not responded to medical therapy. Without surgical intervention the risk of cecal rupture is high for either case. Horses with firm digesta impactions usually reveal a cecum of normal color and wall thickness, with digesta also present in the large colon. Horses with secondary cecal impaction frequently show a grossly distended, taut cecum with a hyperemic, edematous wall and virtually empty ventral large colon. Careful assessment of the integrity and viability of the cecal wall should be performed, because the surgeon needs to decide whether functional cecal motility will return after the operation. The impacted mass of digesta, no matter what its consistency, should be evacuated through a cecal apex typhlotomy.

The surgeon's next consideration is whether to bypass the cecum. The decision is made on the basis of the history and clinical signs leading up to the surgery, assessment of the cecum at surgery, and surgeon experience. A severely distended, hyperemic cecum with thickened walls and no noticeable motility after evacuation of its contents warrants a bypass procedure. Lack of digesta in the right ventral colon adds weight to the belief that cecal motility is abnormal and further supports a bypass procedure. The concern is that dysfunctional cecal motility may not correct to normal motility and that without a bypass procedure, recurrence of the impaction would be likely. This being said, a recent report indicated that typhlotomy and cecal evacuation was used successfully to treat horses with cecal impaction secondary to apparent cecal dysfunction. It could be argued that cases of cecal impaction in hospitalized patients need only a typhlotomy and evacuation because the impaction has occurred in a recognized manner and motility is likely to recover postoperatively with aggressive care. Certainly, if the cecum has normal color and wall thickness and motility is present after removal of the impaction, then the surgeon can conclude that a bypass procedure is not indicated.

Currently, the procedure of choice for bypassing the cecum is the complete ileocolostomy or jejunocolostomy. During the complete bypass procedure, the distal ileum or jejunum is transected and the proximal blind end is then anastomosed to the right ventral colon. Eliminating the cecum from the normal digestive pathway is tolerated well in the long term.

### PROGNOSIS

The prognosis for recovery from cecal impaction depends on the treatment modality, the duration of the impaction, and the type of cecal impaction encountered. Medical therapy provides an excellent chance of resolution of the impaction if treatment is initiated early before the cecum becomes excessively distended. Success rates for medically treated cecal impactions approach 90%. Surgical treatment of cecal impaction has also resulted in excellent outcomes. Typhlotomy and cecal evacuation alone or in combination with complete bypass of the cecum has a good prognosis when patients are operated on before there is evidence of systemic deterioration. In a recent report in which cecal impactions were treated by typhlotomy and

ileocolostomy or jejunocolostomy, 7 of 9 horses lived long-term. Cecal rupture associated with cecal impactions is a significant cause of death and the emphasis is on early recognition of the disease and aggressive treatment.

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## CHAPTER 3.17

# Right Dorsal Colitis

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*Raleigh, North Carolina*

**R**ight dorsal colitis (RDC) is an ulcerative inflammatory disease that affects the right dorsal segment of the colon. The syndrome is characterized by mucosal ulceration of variable severity and thickening, inflammation and edema of the underlying submucosa, and lamina propria. Depending on the duration of the disease, fibrosis may be evident with circumferential stricture. Right dorsal colitis has most commonly been associated with nonsteroidal antiinflammatory drug (NSAID) administration at higher than recommended doses. Right dorsal colitis has been induced in horses by administering phenylbutazone (6 g PO for 5 days) and reducing water intake to half of maintenance requirements. Thus it appears that phenylbutazone administration in the presence of dehydration is a risk factor for RDC. However, it is important to note that the tendency to develop RDC is not limited to horses that receive excessive doses of NSAIDs. Some horses appear to be more sensitive to the toxic effects of NSAIDs, and RDC has occurred in horses that have been given relatively low doses. Most reported cases of RDC are in horses that have received phenylbutazone, but it is unclear whether this reflects a propensity for this NSAID to cause RDC or the relatively common and often chronic use of this drug for musculoskeletal conditions in the horse.

NSAIDs cause mucosal ulceration through inhibition of cyclooxygenase (COX) and suppression of intestinal prostaglandin (PG) production. PGs are critical for mucosal health and maintenance of the epithelial barrier. NSAIDs clearly can disrupt epithelial barrier function, resulting in increased permeability to bacterial products, including endotoxin. Mucosal ulceration and exposure of the lamina propria to luminal microbial products initiates an inflammatory reaction that potentiates mucosal injury. NSAID administration has been linked with a variety of

gastrointestinal (GI) diseases in many species, including gastroduodenal ulcers and colitis. Thus it is thought that RDC is initiated by NSAID-induced injury to the colonic mucosa. Why mucosal injury is limited to the right dorsal colon in RDC remains unclear, however. NSAID-induced generalized colitis has also been reported in horses.

### SIGNALMENT

Many horses with RDC are performance animals with a history of receiving NSAIDs, particularly phenylbutazone. Predilection for the disease has not been noted in any specific age, sex, or breed. The incidence of RDC in horses is unknown but appears to be low.

### CLINICAL SIGNS

RDC may present as either of two forms. The most prominent clinical signs of either form of RDC are colic, lethargy, and anorexia. Acute and often severe colic, fever, depression, anorexia, diarrhea, and signs of endotoxemia characterize the acute form of RDC. Chronic RDC is associated with weight loss, lethargy, anorexia, ventral edema, and chronic intermittent colic. In contrast to acute RDC, chronic RDC is not typically associated with overt diarrhea, although the feces may be soft and unformed. Significant hypoproteinemias attributable mainly to hypoalbuminemia is a hallmark of the disease. However, hypoglobulinemia may also contribute to hypoproteinemia. Hypoproteinemia is likely a result of protein loss from the ulcerated right dorsal colon and may occur in both acute and chronic RDC. Hypoproteinemia may be severe enough to cause peripheral (usually ventral) edema. Horses with acute RDC may survive the acute episode only to develop the chronic form of the disease with progressive edema and intermittent colic.



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## DIAGNOSIS

Clinicopathologic findings are not often helpful in diagnosing RDC. The peritoneal fluid analysis and cytologic examination may reveal nonspecific evidence of inflammation. The complete blood count may reveal a neutropenia, neutrophilia, or hyperfibrinogenemia. Anemia is common, but it is unclear whether the cause is blood loss or chronic inflammation. Hypoalbuminemia is a hallmark of the disease and may be severe (less than 1.5 g/dl). Hypocalcemia may be evident but usually reflects the hypoalbuminemia and ionized calcium may be normal.

Presumptive diagnosis is usually based on clinical signs and a history of NSAID administration. Ultrasonography (3.5- to 5-MHz transducer at the right twelfth-fifteenth intercostal spaces below the margin of the lung axial to the liver) may reveal a thickened right dorsal colon (>0.6 cm) and evidence of colonic edema (Figure 3.17-1). However, ultrasonographic examination does not appear to be particularly sensitive for the diagnosis of RDC. Thus alternative diagnostic tests have been sought. A technique has been described in which white blood cells are purified from whole blood, labeled with technetium-99m hexamethylpropyleneamine oxime, and injected via the intravenous (IV) route back into the donor. Nuclear scintigraphy is then used to detect uptake of the radiolabeled white blood cells in inflamed tissues. This technique has been used to identify inflammation of the right dorsal colon and diagnose RDC in two horses with compatible clinical signs. However, in spite of the imaging modalities available, definitive diagnosis often requires laparoscopy or exploratory laparotomy. Endoscopic examination should be performed to rule out gastric ulcer disease.

## THERAPY

Rest, dietary management, and discontinuation of NSAID administration are successful for resolving many cases of



**Figure 3.17-1** Ultrasonographic image of the colon in a horse with chronic right dorsal colitis. Note the marked thickening of the colon (1.59 cm). The layers of the wall are readily distinguished because of edema associated with inflammation and hypoproteinemia. The image was obtained with a 3.5-MHz, sector-scanning transducer at the right thirteenth intercostal space ventral to the margin of the lung. Display depth is 18 cm. The dorsal side is to the left.

RDC. Dietary management consists of eliminating long stem roughage (hay) from the diet and feeding exclusively a complete pelleted diet that contains at least 30% dietary fiber for at least 3 months. The rationale behind this recommendation is to reduce the mechanical load on the right dorsal colon. Frequent meals (4-6 times/day) are recommended. Small amounts of fresh grass may be tolerated but should be avoided if possible. Corn oil (1 cup q12-24h) can be added to the pellets to increase the caloric intake without the addition roughage or grain. Psyllium mucilloid can be added to the diet (5 tablespoons q12-24h) to increase the production of short-chain fatty acids (SCFAs) in the colon. Amylase-resistant fermentable fiber such as psyllium is hydrolyzed by colonic bacteria to SCFAs, which represent a major energy source for colonocytes. SCFAs hasten epithelial maturation and stimulate salt and thus fluid absorption in the colon, improve the clinical course of ulcerative colitis, and hasten colon healing. Of the SCFAs, butyrate may be the most clinically relevant because it is the most potent of the SCFAs. Psyllium is itself a source of butyrate in the colon and also promotes the movement of amylase-sensitive carbohydrates into the distal colon, which are then fermented to SCFAs. Thus psyllium is thought to be clinically useful for promoting mucosal healing in RDC.

In addition to the nutritional management described above, several pharmacologic approaches are used to hasten mucosal healing. The first is to replace PGs that are missing as a result of NSAID administration. Misoprostol (2 µg/kg PO q8h), a synthetic PGE<sub>1</sub> analog, has been shown in several species to prevent NSAID-induced mucosal injury, to enhance mucosal healing in NSAID-injured intestinal tissue, and promote recovery in experimental models of colonic inflammation. However, the efficacy of misoprostol used to hasten mucosal healing is clinically unproven in equine colitis. A synthetic PGE<sub>2</sub> analog has been demonstrated to prevent GI lesions associated with experimental phenylbutazone toxicosis in ponies. The primary drawbacks of PG analogs such as misoprostol are drug side effects including sweating, diarrhea, abdominal cramping, and abortion in pregnant mares.

Sucralfate (22 mg/kg PO q6h) has been advocated to promote the healing of ulcerated mucosa in the right dorsal colon. The evidence supporting this treatment is derived from human studies in which sucralfate relieves discomfort and inflammation associated with colitis and radiation-induced enteropathy. Although sucralfate requires an acidic environment to optimally bind ulcerated mucosa, significant binding to ulcerated colonic mucosa occurs. Whether oral administration delivers effective concentrations of sucralfate to the right dorsal colon in horses is not known, and administration by enema is not feasible in horses with RDC. Thus, no direct evidence exists to support the use of sucralfate to treat RDC in horses. Nevertheless, sucralfate has few side effects and is not contraindicated for the treatment of RDC in horses.

Metronidazole (15 mg/kg PO q6-8h) has also been advocated as a treatment for RDC in horses. The benefit of metronidazole is not from its antimicrobial activity, but from the antiinflammatory properties. Metronidazole is useful for reducing inflammation and clinical severity of Crohn's disease in humans. Although metronidazole's an-

tiinflammatory properties are clearly established, no evidence exists that the drug hastens recovery from RDC in horses. Sulfasalazine is also used to treat inflammatory bowel disease in humans. Like metronidazole, sulfasalazine has not been evaluated for use in horses with NSAID colitis. The ability of sulfasalazine and its metabolites to inhibit cyclooxygenase (COX) may contraindicate its use in horses with RDC; however, the potency of sulfasalazine as a COX inhibitor appears to be low and to be outweighed by the antiinflammatory effects in inflammatory bowel disease.

Hypoproteinemia can be treated with plasma infusion (5-10 ml/kg IV per day) to boost plasma protein concentration and plasma oncotic pressure. Plasma administration will not only reduce peripheral edema but may also reduce colonic edema associated with RDC. Plasma may thus speed healing of the right dorsal colon. Plasma is indicated if tissue edema is evident or if the plasma albumin concentration is less than 2 g/dl. Even if normal plasma protein concentrations are present, if endotoxemia is present plasma may be beneficial to improve cardiac output and tissue perfusion. Other colloids such as hetastarch (5 ml/kg/day IV) may be useful to combat tissue edema from low plasma oncotic pressure if plasma is not available or is cost prohibitive. Purified albumin preparations are also available for IV use. The half-life of exogenous plasma protein and carbohydrate colloids is very short compared with the recovery time for horses with RDC. Thus plasma and other colloids are generally used to boost plasma protein concentration and oncotic pressure during acute episodes of RDC and are not practical for long-term management of the disease.

Pain management can be challenging in horses with RDC, because the disease precludes the use of most NSAIDs to control pain. Newer NSAID that specifically target the COX2 (the isoform of COX induced by inflammation) but have little activity against COX1 (the "house-keeping" COX) may be useful analgesics that spare the GI mucosa. For example, etodolac (10-15 mg/kg IV or PO q24h) has analgesic properties in horses. However, its specificity for COX2 in horses is unproven; thus it is advisable to avoid the use of any NSAID in horses with RDC. Butorphanol (0.05-0.1 mg/kg IM or IV) is used commonly to relieve pain in horses with RDC. Butorphanol infusion

may also be used to control persistent abdominal pain in horses with RDC. A loading dose (0.1 mg/kg IV) is administered IV followed by infusion of 13.2  $\mu$ g/kg/hr in isotonic crystalloid fluid such as lactated Ringer's solution. IV infusion of lidocaine (1.3 mg/kg IV loading dose administered slowly during a 5-minute period followed by 3 mg/kg/hr infusion in isotonic crystalloid fluids) is also an effective analgesic in horses with colic. Care should be taken to monitor horses receiving a lidocaine infusion for adverse effects such as seizures or collapse that indicate toxicity.

In horses with RDC that have severe or uncontrollable colic pain or pain that is unresponsive to medical therapy, exploratory laparotomy and resection or bypass of the right dorsal colon may be indicated. Horses with acute RDC may require IV fluid therapy for dehydration and systemic hypotension from diarrhea and endotoxemia. Other therapies for endotoxemia may also be indicated.

Clinical signs, particularly change in weight, appetite, and frequency of colic episodes, are useful to monitor response to therapy. However, an increase in serum albumin concentration is perhaps the most sensitive indicator of right dorsal colon healing. Ultrasonographic evaluation of right dorsal colon thickness is also useful to monitor progression. Recovery from RDC may take months. Complications of RDC include laminitis, colon rupture, and colonic infarction. The prognosis for horses with either acute or chronic RDC is guarded.

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## CHAPTER 3.18

# Infiltrative Bowel Diseases

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**I**nfiltrative bowel disease (IBD) is a dysfunction of the gastrointestinal (GI) tract caused by infiltration of the mucosa and submucosa with populations of eosinophils, lymphocytes, macrophages, plasma cells, or basophils. Clinical signs of IBD vary but may include colic, weight loss, lethargy, diarrhea, and dependent edema. Infiltrative bowel disease is usually associated with a protein-losing enteropathy, and malabsorption of nutrients. Etiologic agents have been identified in some cases of IBD in the horse. These agents include mycobacteria, *Lawsonia intercellularis*, intestinal nematodes, and hairy vetch. The following four syndromes of idiopathic IBD in the horse are recognized: granulomatous enteritis, lymphocytic-plasmacytic enterocolitis, multisystemic eosinophilic epitheliotropic disease, and idiopathic eosinophilic enterocolitis (EC). Signalment, clinical signs, clinicopathologic findings, and gross pathologic lesions of these diseases are sometimes characteristic of a particular IBD, but in general these features are similar for most horses with any form of IBD, and morphologic or etiologic diagnosis is made by histologic examination of affected intestinal tissue. The prevalence of clinical and clinicopathologic signs and postmortem lesions of these diseases are compared in Tables 3.18-1, 3.18-2, and 3.18-3.

### GRANULOMATOUS ENTERITIS

Granulomatous enteritis (GE) has been compared with Crohn's disease in human beings because the histopathologic lesions of both diseases are similar. GE has been reported to occur most frequently in Standardbred horses, in some cases in related horses, a finding that indicates a possible genetic predisposition to the development of the disease. Affected horses are usually young and are almost invariably examined because of weight loss and anorexia. Only one third of horses in reported cases had signs of GI disease other than weight loss. The presence of skin disease in horses affected with multisystemic eosinophilic epitheliotropic disease is a feature that is often considered to distinguish multisystemic eosinophilic epitheliotropic disease from GE, but horses with GE may also have skin lesions usually involving the head and limbs, especially the coronet.

The most consistent clinicopathologic finding of horses with GE is hypoalbuminemia. Horses with IBD experience enteric loss of proteins of all molecular weights, but because globulins tend to be produced faster than albumin, the most striking feature of IBD in the horse is hypoalbuminemia. Most horses with GE are anemic, but anemia may not be evident because of a diminished plasma vol-

ume caused by low plasma albumin concentration. Plasma transfusion may cause a marked drop in the packed cell volume of horses with GE.

Carbohydrate absorption tests of horses with GE usually demonstrate abnormal absorption of either glucose or xylose. Malabsorption of carbohydrates is attributed to severe villous atrophy that occurs diffusely throughout the small intestine. Some horses with GE may have a normal carbohydrate absorption test, presumably because the disease has not progressed to the point where villous absorptive capacity is exceeded, or because intestinal lesions are so focal that they do not interfere with absorption.

Rectal biopsy of horses with GE may contribute to the diagnosis; about one half of affected horses in reported cases had lesions in rectal biopsy samples that were typical of the disease. If tissue obtained by rectal biopsy is not diagnostic, celiotomy for biopsy of grossly abnormal tissue is likely to provide the diagnosis. Sheets of macrophages or epithelioid cells and circumscribed granulomas in the mucosa or submucosa are seen during histologic examination of diseased tissue.

Prognosis for survival of horses with GE is poor. A few horses with GE have been reported to respond favorably to treatment with dexamethasone, but long-term survival with any medical treatment—including corticosteroids, anabolic steroids, antibiotics, iodochlorhydroxyquin, and anthelmintic drugs—has not been reported. Horses with GE do not respond to administration of drugs used to treat Crohn's disease in human beings, such as salicylazosulfapyridine and methylsulfapyridine. Because horses with disease of the intestinal tract and horses that are immunosuppressed are at risk of developing pulmonary aspergillosis, horses treated with corticosteroids for IBD may be at increased risk of developing pulmonary aspergillosis. Metronidazole, which is both an antibiotic and an antiinflammatory agent, is beneficial in treatment of some human beings with Crohn's disease. There are no reports concerning the use of orally administered metronidazole for treatment of horses with GE, but metronidazole formulated for oral administration is inexpensive and is well tolerated by horses.

Two horses with GE responded favorably to removal of grossly affected ileum and several meters of distal jejunum, with one of these horses surviving for at least 12 years after surgery as an apparently healthy horse. Surgical treatment of most horses with GE is unlikely to be beneficial, however, because gross intestinal lesions are usually diffuse and involve long segments of intestine.

The cause of GE is unknown in most reported cases even when a detailed history, tissue cultures, and histo-

Table 3.18-1  
Prevalence of Clinical and Clinicopathologic Signs of Horses Reported to Have GE, LPE, MEED, or EC

Disease	Weight Loss	Diarrhea	Colic	Dermatitis	Anemia	Low Serum Albumin	Low Serum Protein	Malabsorption of Glucose or Xylose	Elevated GGT	Diagnosis Indicated by Rectal Biopsy
GE	98 (46/47)	30 (14/47)	11 (5/47)	11 (5/47)	87 (41/47)	91 (42/46)	64 (29/46)	90 (19/21)	0 (0/15)	50 (9/18)
LPE	95 (19/20)	35 (7/20)	20 (4/20)	0 (0/20)	10 (2/20)	55 (11/20)	35 (7/20)	82 (14/17)	5 (1/20)	Unlikely to be diagnostic
MEED	100 (46/46)	63 (29/46)	4 (2/46)	63 (29/46)	10 (4/41)	79 (30/38)	58 (23/38)	38 (8/21)	73 (11/15)	50 (6/12)
EC	7 (1/14)	0 (0/14)	100 (14/14)	0 (0/14)	0 (0/14)	14 (2/14)	14 (2/14)	Not determined	0 (0/14)	Unlikely to be diagnostic

GE, Granulomatous enteritis; LPE, lymphocytic-plasmocytic enteritis; MEED, multisystemic eosinophilic epitheliotropic disease; EC, idiopathic eosinophilic enterocolitis; GGT,  $\gamma$ -glutamyl transferase.

Table 3.18-2

**Gross Lesions in Horses Affected with Idiopathic Inflammatory Bowel Diseases**

Disease	Lesions of Small Intestine	Lesions of Large Intestine	Distribution of Intestinal Lesions	Pancreatitis	Other Organs with Gross Lesions
GE	Common; only 2 of 42 horses without gross lesions	Common; 21 of 42 horses	Usually diffuse (reported as segmental in only 4 of 47 horses)	Not reported	Skin and mesenteric lymph nodes
LPE	Common; 13 of 16 horses	Common; 7 of 16 horses	Segmental/diffuse; numbers not specific	None	Mesenteric lymph nodes
MEED	Common; 19 of 26 horses	Common; 20 of 26 horses	Segmental/multifocal	Common; 13 of 23 horses	Skin, oral cavity, esophagus, salivary glands, liver, lung, mesenteric lymph nodes
EC	Common; number not clear in report of 11 horses	Common; number not clear in report of 11 horses	Segmental/diffuse; circumferential mural bands	None	None

GE, Granulomatous enteritis; LPE, lymphocytic-plasmacytic enterocolitis; MEED, multisystemic eosinophilic epitheliotropic disease; EC, idiopathic eosinophilic enterocolitis.

Table 3.18-3

**Microscopic Lesions of Horses Affected with Idiopathic Inflammatory Bowel Disease**

Disease	Cell Type	Villous Atrophy
GE	Aggregates of macrophages and epithelioid cells; giant cell macrophages occasionally present	Constant
LPE	Infiltration of the lamina propria with lymphocytes and plasma cells	Constant
MEED	Infiltration of mucosa and submucosa with eosinophils (or rarely, basophils) lymphocytes, and macrophages	Rare
EC	Infiltration of all layers of intestine with eosinophils or eosinophils and lymphocytes; fibrosis	

GE, Granulomatous enteritis; LPE, lymphocytic-plasmacytic enterocolitis; MEED, multisystemic eosinophilic epitheliotropic disease; EC, idiopathic eosinophilic enterocolitis.

logic examination of affected tissues, including electron microscopy, are used in the investigation. Although controversial, there is some evidence that human IBD is caused by infectious agents. There is some evidence that exposure to *Mycobacterium paratuberculosis* during the postnatal period is a cause of Crohn's disease. Natural or experimental infections of *M. paratuberculosis* in horses results in microscopic granulomatous intestinal lesions similar to those found in Crohn's disease.

**LYMPHOCYTIC-PLASMACYTIC ENTEROCOLITIS**

Few reports exist of lymphocytic-plasmacytic enterocolitis (LPE) in horses, but these reports indicate that this disease has no predilection for horses of any age or breed, or for ei-

ther sex. Horses with LPE are usually examined for weight loss, and some affected horses also have diarrhea or recurrent signs of colic. Most horses with LPE have abnormal absorption of carbohydrates. Anemia and hypoalbuminemia are not consistently found in horses with LPE. Lymphoid and plasma cells may be found in rectal tissue of horses with various intestinal diseases, including granulomatous disease, cyathostomiasis, and malignant lymphoma, and therefore the finding of a lymphocytic proctitis on rectal biopsy, particularly if mild, may not justify a diagnosis of LPE.

Treatment of horses with LPE is likely to be unsuccessful even though some horses may experience brief resolution of diarrhea when treated with corticosteroids. In all published reports of horses with LPE, affected horses were euthanized because of poor condition or lack of response to therapy.

In other species, such as the dog, LPE is hypothesized to represent a nonspecific intestinal immune response to a variety of etiologic agents that cause intestinal damage. For the clinician, distinguishing between GI lymphosarcoma and LPE in dogs by histologic examination alone is difficult. As in the dog, LPE in the horse may be a prelymphomatous intestinal disease.

### MULTISYSTEMIC EOSINOPHILIC EPITHELIOTROPIC DISEASE

In various reports, multisystemic eosinophilic epitheliotropic disease (MEED) has been termed eosinophilic gastroenteritis, EC, eosinophilic granulomatosis, hyper-eosinophilia syndrome, and exfoliative eosinophilic dermatitis and stomatitis. This IBD is characterized by eosinophilic infiltration not only of the intestine but also of other organs. Infiltration of intestine and other tissues with basophils causes signs similar to MEED and may be a variant of MEED. The terms *eosinophilic gastroenteritis* or *eosinophilic enterocolitis* should be used to describe an IBD in which lesions are restricted to the GI tract. Because clinical features and prognosis for horses with eosinophilic infiltrates that are restricted to the intestine are different from horses that have both intestinal and extraintestinal infiltration of eosinophils, MEED and EC should be considered separate diseases.

As with GE, most reported cases of MEED involve young horses, and Standardbreds are the breed most often affected. Dermatitis that resembles pemphigus foliaceus is a common feature of horses with MEED. Affected horses often have an exudative dermatitis on the face, limbs, and ventral portion of the abdomen and ulcerations of the coronet and oral cavity. Unlike horses with GE, horses with MEED are seldom anemic. The white blood cell count of affected horses is usually normal, but some affected horses have a marked eosinophilia. Horses with MEED are commonly affected with disease of the liver and pancreas and serum concentrations of  $\gamma$ -glutamyl transferase are often elevated. Ultrasonographic examination or biopsy of the liver may aid in diagnosis of liver disease associated with MEED. The diagnosis of MEED can be made by histologic examination of rectal mucosa obtained by biopsy in many affected horses. Rectal biopsies should be interpreted with caution because eosinophilic infiltrates in rectal mucosa and submucosa are found in normal horses. The presence of eosinophilic granulomas, associated with vasculitis and fibrinoid necrosis of intramural vessels in rectal tissue is considered diagnostic of MEED. Because Bouin's solution makes eosinophils less conspicuous, rectal biopsy tissue should be fixed in formalin. Most horses with MEED are likely to have a normal carbohydrate absorption test because lesions of MEED are more likely to involve the large intestine than the small intestine.

Treatment of horses affected with MEED with antimicrobial and anthelmintic drugs and corticosteroids is nearly always unsuccessful, although one horse survived for at least 18 months with repeated injections of dexamethasone. In that report, parenteral administration of corticosteroid was advised because of potential malabsorption of orally administered medication. One horse that failed to respond to parenterally administered dexametha-

sone responded briefly to orally administered hydroxyurea, an antineoplastic drug used to treat humans with hyper-eosinophilia syndrome. Anthelmintics that have larvicidal activity may also be indicated for treatment of horses with MEED, because nematode larvae have been speculated to play a role in the pathogenesis of this disease.

The etiology of MEED is unknown despite electron microscopic, epidemiologic, and bacteriologic studies. Authors of some reports have speculated that the cause of MEED is recurrent episodes of type I or immediate hypersensitivity reactions evoked by dietary, inhaled, or parasitic antigens. Migrating nematodes have also been speculated to cause MEED. Parasites contain endogenous factors that attract eosinophils, and many of the organs affected by eosinophilic granulomas (e.g., pancreas, liver, and colon) are involved in the life cycle of several nematodes.

### IDIOPATHIC EOSINOPHILIC ENTEROCOLITIS

For some horses with IBD, eosinophilic infiltrates are restricted to the intestine. These horses show different clinical signs and have a better prognosis for survival than do horses with MEED, thus justifying a separate classification as idiopathic eosinophilic enterocolitis (EC). The primary clinical sign of horses with EC is colic rather than weight loss. Affected horses are unlikely to be anemic, hypoalbuminemic, or hypoproteinemic. Information on carbohydrate absorption is incomplete. EC is unlikely to be diagnosed by rectal biopsy because eosinophilic infiltrates (as opposed to eosinophilic granulomas found in rectal mucosa of horses with MEED) can be found in the rectal mucosa of normal horses.

EC is diagnosed by histologic examination of diseased intestine obtained during postmortem examination or exploratory celiotomy. All layers of small or large intestine are diffusely infiltrated with eosinophils or an equal mixture of eosinophils and lymphocytes. During exploratory celiotomy, circumferential mural bands are found in the small or large intestine of some horses. These bands are thought to result from stimulation of fibrous connective tissue by enzymes elaborated by eosinophils and are considered pathognomonic for EC.

Horses with EC may respond to orally administered corticosteroids for 30 days to 6 months. Anthelmintics with larvicidal activity are also administered to some horses with EC because the presence of eosinophils in intestinal tissue is often attributed to parasitism. Recurrence of clinical signs after discontinuation of treatment is rare. Horses with intestinal mural bands may respond to resection of affected intestine. Recurrent signs of colic in horses with intestinal mural bands may also resolve after administration of corticosteroids, frequent small meals of a pelleted complete ration, and analgesics for episodes of colic.

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## CHAPTER 3.19

# Laparoscopic and Ultrasonographic Imaging of the Gastrointestinal Tract

A. T. FISCHER, JR.  
*Chino, California*

**I**maging of the gastrointestinal (GI) tract in horses is difficult because of the animals' large size and the limitations inherent in the use of diagnostic medical equipment designed for human beings. Improvements in ultrasound technology have helped clinicians working with horses to image deeper into the abdominal cavity of horses with more detail. Increasing familiarity with laparoscopic anatomy and techniques has allowed a more thorough evaluation of the horse's GI tract, particularly for evaluation of horses with colic and weight loss.

### ULTRASONOGRAPHIC EVALUATION OF THE ABDOMEN

Abdominal ultrasonography is perhaps the most useful diagnostic imaging modality for evaluation of the horse's GI tract that is currently available. This method can be used to diagnose peritonitis, gastric abnormalities, peritoneal effusion, diaphragmatic hernias, abdominal neoplasia, small intestinal strangulation obstructions, intussusceptions of the small and large intestine, and renosplenic incarceration of the large colon. The abdominal cavity should be systematically examined in all horses whenever ultrasonographic evaluation is performed. The abdomen should be examined from the line of diaphragmatic reflection ventrally on both sides. A low-frequency ultrasound transducer (2- to 3.5-MHz) is used to obtain maximal depth of penetration during the examination, although higher-frequency transducers may be used in foals. In most horses liberal application of alcohol wets the horse's hair coat sufficiently to allow

penetration of the ultrasound waves, thus clipping of the hair coat is unnecessary.

The liver is imaged on the left side of the horse immediately caudal to the heart and on the cranial right side below the line of diaphragmatic reflection. The liver should be evaluated for neoplasia, hepatic enlargement or atrophy, and cholestasis resulting from biliary calculi. The stomach is imaged from the left side of the horse between the eleventh and thirteenth intercostal spaces at the level of the shoulder. The stomach is located deep to the spleen; the clinician can identify it by looking dorsal to the splenic hilus and its large splenic vein. The greater curvature of the stomach is recognized as a hyperechoic line curving towards the skin surface beneath the spleen. The spleen may be displaced caudally or may be obscured by gastric distention. Distention of the stomach, gastric impaction, adequacy of nasogastric decompression, and gastric squamous cell carcinoma have been assessed with ultrasonography.

The duodenum is examined from the right side of the horse below the line of diaphragmatic reflection and is located ventral to the right kidney and caudate lobe of the liver. The duodenum is evaluated for distention, thickening, and motility. The rest of the small intestine is imaged more ventrally in the abdominal cavity. Small intestinal strangulation obstructions are characterized by edema, distention, and lack of motility. It is not usually possible to make an anatomic diagnosis of the cause of these small intestinal obstructions. The small intestine is considered to be thickened when its wall thickness is greater than 3 cm. Peritonitis is characterized by thickening of the



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small intestine, varying amounts of distention, and normal to decreased motility. Intussusceptions of the small intestine are recognized by a target or bull's-eye appearance. A thickened small intestine may be noted oral to adhesions in horses and can also be noted in horses with granulomatous bowel disease and hypoproteinemia. The inguinal canals of horses with suspected inguinal herniation may be examined with ultrasonography to assess for the presence of incarcerated small intestine.

Disorders of the large colon may also be diagnosed with ultrasound. Displacements of the large colon into the nephrosplenic space are noted by the inability to view the left kidney when imaging through the left flank of the horse. The spleen is normally imaged adjacent to the left body wall with the left kidney noted immediately underneath it. In horses with nephrosplenic entrapment of the large colon, a hyperechoic shadow indicating the large colon will be seen where the spleen normally is and the left kidney will not be visible. Inability to image the left kidney is not always diagnostic for nephrosplenic entrapment, however. In some horses the large colon will be lateral to the spleen, which will create this ultrasonographic appearance, but the colon will not be trapped over the nephrosplenic ligament. A thickened large colon will occasionally be seen in horses with colonic displacements, and splenic congestion and dilation of the splenic vessels will also be seen in some of these horses. Repeated ultrasonographic examination of these horses after surgical repositioning will demonstrate a normal appearing spleen and vasculature.

Enterolithiasis is not amenable to diagnosis by ultrasonography. Obstructing enteroliths are most commonly located in the right dorsal or transverse colon or proximal small colon and are usually not in areas accessible by ultrasonography. Enteroliths reflect ultrasound waves similar to gas-distended bowel and are therefore indistinguishable. Gas within the bowel lumen prevents transmission of ultrasound waves, limiting penetration and observation of deeper structures.

Cecocolic and cecocolic intussusceptions may be observed ultrasonographically in the cranial right ventral abdomen. Cecocolic intussusceptions are oval and measure approximately 10 to 15 cm in diameter. The bowel is edematous with hyperechoic margins that are surrounded by intraluminal fluid. Cecocolic intussusceptions may be differentiated from cecocolic intussusceptions by identifying the cecal tip in the right ventral colon. Peritoneal effusion is commonly noted in these horses.

Peritoneal effusion is readily recognized with abdominal ultrasonography. The bowel is separated from the abdominal wall and may be floating within the abdominal cavity. Horses with a ruptured viscus have hyperechoic abdominal fluid with echogenic foci present, and the bowel wall is thickened. Abdominal ultrasonography can be used to localize pockets of abdominal fluid for abdominocentesis and to minimize the chance of lacerating the spleen or other viscera. If no fluid is seen on ultrasonography, abdominocentesis should still be attempted because fluid is frequently present. Hemoperitoneum is diagnosed by imaging echogenic fluid that swirls on ballottement.

Abdominal ultrasonography is less invasive than abdominal palpation per rectum and is more accurate for di-

agnosis of some disorders (i.e., small intestinal strangulation obstruction). Abnormalities noted on abdominal ultrasonographic examination can frequently lead to earlier surgical intervention and, possibly, improved outcomes.

## LAPAROSCOPIC EVALUATION OF THE ABDOMEN

Indications for laparoscopic evaluation of the abdominal cavity include weight loss, inappetence, visceral biopsy, acute and chronic colic, suspected intraabdominal infection or neoplasia, and further characterization of abnormalities noted on abdominal palpation per rectum or ultrasonography. A 30-degree, 57-cm laparoscope is preferred for exploratory laparoscopy. The laparoscope is connected to a 300-W Xenon light source and a video camera. A high-flow (10 L/min) carbon dioxide (CO<sub>2</sub>) insufflator should be available.

The equine GI tract may be evaluated laparoscopically with the horse standing or anesthetized. The choice of position is usually dictated by the region the clinician wishes to evaluate. An example would be a horse with an ultrasonographically detected abnormality of the cranial abdomen that would be best examined laparoscopically with the horse in dorsal recumbency, possibly with the use of Trendelenburg positioning. If practical, horses should be fasted for 24 hours before laparoscopic evaluation, although this is obviously not feasible when an emergency evaluation is necessary. The horse is restrained in standing stocks or anesthetized and the appropriate area for laparoscopic evaluation is prepared for aseptic surgery. Perioperative antibiotics and nonsteroidal antiinflammatories are administered, and tetanus prophylaxis is provided. In standing horses, local anesthesia is provided subcutaneously and intramuscularly at the sites of trocar and instrument insertion. The left flank region is usually explored first to minimize the chances of cecal perforation during trocar insertion. The trocar cannula assembly should be inserted through the middle of the paralumbar fossa at the level of the crus of the internal abdominal oblique muscle aiming at the contralateral coxofemoral joint. The abdomen should be examined in a systematic pattern. The liver, stomach, and spleen are observed in the cranial left abdomen along with the diaphragm. As the laparoscope is brought to the middle of the left abdominal cavity, the left kidney, nephrosplenic ligament, and root of the mesentery can be seen. Isolated segments of small intestine and small colon are noted. The large colon is usually ventral to these structures and therefore not always seen on the left side of the horse. From the caudal perspective, the urogenital structures (mesovarium, ovary, and uterus in females and mesorchium and vas deferens in males) can be seen. The urinary bladder is observed between the two inguinal rings, and the rectum can be seen passing caudally over the urinary bladder. On the right side of the horse, the diaphragm and liver can be noted cranially. The duodenum, right kidney, and cecal base are noted in the midabdomen. The clinician can examine the epiploic foramen by carefully going through it with the laparoscope. The large colon is typically seen proceeding forward from the cecum. Isolated segments of small intestine and small colon can be noted in the midabdomen to

caudal abdomen. The right side urogenital structures are observed when looking caudally. The clinician can view the rectum by looking dorsal to the urinary bladder.

### Abnormal Laparoscopic Findings

Although laparoscopic evaluation is most commonly performed for horses with a history of chronic colic or weight loss, exploration of horses with acute colic may be performed when the owner cannot afford an exploratory celiotomy under general anesthesia and confirmation of a surgical lesion or ruptured viscus is desired. For example, mares may be evaluated for acute colic following parturition, when bruising of the small colon, uterus, and other intestinal segments may be noted. Rupture of the uterus and tearing of the mesocolon with vascular compromise to the small colon may also be observed. Visceral rupture may be inferred by finding evidence of contamination of the abdominal cavity, even though the exact site of the rupture may not be found.

Small intestinal strangulation obstructions have been noted on laparoscopic examination. The affected bowel is reddened and edematous and will become blue to black as the strangulation proceeds. The path of the small intestine may be followed laparoscopically with the aid of Babcock forceps in the anesthetized horse. The clinician can diagnose proximal enteritis by seeing discolored edematous descending duodenum on the right side of the abdomen. Large intestinal displacements may be diagnosed with laparoscopy. In these horses, the intestine is noted to be in an abnormal location, such as the presence of the pelvic flexure on the right side of the abdomen. Colonic volvulus and strangulation obstructions may also be diagnosed by seeing discolored edematous large colon in an abnormal location. Diaphragmatic hernias may be diagnosed either by laparoscopy or thoracoscopy. Suction should be available to evacuate the resulting pneumothorax.

Trauma and penetrating wounds into the abdominal cavity may also be evaluated laparoscopically. It is important to select an entry site remote to the penetrating wound to optimize the visual field and avoid increasing contamination of the abdominal cavity.

Laparoscopic findings in horses with chronic colic include neoplastic and infectious conditions. For instance, gastric squamous cell carcinoma has been noted. Neoplasia in other abdominal structures may be found, and laparoscopically guided biopsies may provide diagnostic information on these tumors. Thickened small intestine may be noted as a result of *Mycobacterium* spp. infections or oral to adhesions or strictures. Adhesions involving sections of the GI tract or other abdominal organs may be seen and can frequently be treated laparoscopically. Peritonitis and abdominal abscesses may be evaluated laparoscopically. Culture samples may be obtained and drains may also be inserted under laparoscopic visualization.

Laparoscopic and ultrasonographic imaging of the GI tract have improved clinicians' understanding of GI anatomy and function. These diagnostic modalities have improved the decision making process for proceeding to an exploratory celiotomy or obtaining a diagnosis regarding intraabdominal problems. Further experience with both diagnostic modalities will likely increase the clinician's ability to accurately diagnose and treat problems of the horse's GI tract.

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## CHAPTER 3.20

# Rectal Tears: Initial Management and Liability

ANTHONY T. BLIKSLAGER  
*Raleigh, North Carolina*

**R**ectal tears are a well-documented risk of rectal palpation in horses, and yet equine veterinarians tend to be poorly prepared when faced with blood on a rectal sleeve. In fact, rectal tears are a potential complication of any rectal palpation, regardless of the experience of the veteri-

narian and the circumstances of the rectal palpation. Furthermore, claims of negligence are probably more likely to occur because of poor medical management of the tear rather than creation of the tear itself. Therefore veterinarians must understand exactly what to do when a rectal tear occurs.

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narian and the circumstances of the rectal palpation. Furthermore, claims of negligence are probably more likely to occur because of poor medical management of the tear rather than creation of the tear itself. Therefore veterinarians must understand exactly what to do when a rectal tear occurs.

## LIABILITY

Complications of rectal tears account for approximately 7% of the malpractice claims received by the Professional Liability Insurance Trust of the American Veterinary Medical Association (AVMA). Nonetheless, veterinarians are not required to inform clients of the risk of rectal palpation and do not typically seek informed consent from owners before performing a rectal palpation. However, explaining the risks and consequences of rectal palpation can protect the veterinarian from liability. A simple, one-page information sheet can be given to owners before examination of the horse or distributed with a new-client information packet. In some horses rectal palpation simply may carry too great a risk. For example, 31.7% of rectal injuries reported to the AVMA liability trust between 1979 and 1994 were in Arabian horses, and young horses (1 to 5 years) and stallions also were overrepresented. Therefore a young stallion, particularly an Arabian, carries a high risk for rectal injury.

Regardless of the issue of informed consent, veterinarians are not negligent if a rectal tear occurs as long as they have taken adequate precautions against causing rectal injuries. Such precautions include adequate restraint and/or sedation of the horse, use of adequate lubricant, and a nonforceful approach (i.e., basic common sense). The degree of restraint is dictated by the situation and is the responsibility of the veterinarian. If stocks are available, they should be used. If not, a knowledgeable person, such as a veterinary technician, should hold the horse, and sedation or a twitch should be used if needed.

## INITIAL APPROACH AND MANAGEMENT

An organized approach should be taken in every case in which blood is observed on the rectal palpation sleeve. First, the owner should be apprised of the situation before further work-up. Subsequently, the horse should be sedated (e.g., xylazine 0.3 to 0.5 mg/kg IV), and the rectum itself examined. Palpating the rectal mucosa without a rectal sleeve, with liberal amounts of lubricant, is the best way to perform the exam. Although practitioners are concerned about exacerbating the tear during further examination, palpation of the rectal mucosa with fingertips should not increase tension on the tear. The rectum also can be observed with an endoscope after air insufflation of the rectum or via a transparent speculum.

The goal of these examinations is to determine the grade of the rectal tear (Table 3.20-1). Grade 1 tears, which are superficial lacerations or abrasions of the rectal mucosa, can be difficult to detect digitally because of the lack of a marked defect but can be readily distinguished by endoscopy (Figure 3.20-1). These tears can be treated on the farm without the need for referral, unless a question exists regarding the extent of the tear. Grade 2 tears are probably the least common form of rectal tears and may not be readily detected because of the lack of rectal bleeding that would typically indicate a need for further examination. Grade 2 tears may present as rectal impactions because of the formation of a rectal diverticulum. Grade 3 tears, which involve all layers of the rectal wall except the serosa or mesocolon (see Table 3.20-1), should be referred for advanced medical and surgical treatment. Horses with grade



**Figure 3.20-1** Transrectal endoscopic view of a grade 1 rectal tear. Note the circular defect in the dorsal wall of the small colon (arrows) that extends no deeper than the mucosa. The tear was of 5 days' duration and had begun to contract and granulate.

**Table 3.20-1**  
**Classification of Rectal Tears**

Grade	Description	Treatment Options
1	Tears limited to the mucosa	Medical care: antibiotics, antiinflammatories, dietary modification
2	Tears limited to the muscular layers (mucosa intact)	No specific therapy; observation for development of rectal impaction
3	Tears that rupture all layers of the rectum except the serosa (grade 3a) or mesocolon (grade 3b)	1. Frequent rectal evacuation (only for tears $\leq 10$ cm in diameter) 2. Direct suture 3. Loop colostomy 4. Rectal liner
4	Full-thickness tears	Euthanasia

4 tears in most cases should be euthanized. However, if a question exists regarding the extent of a rectal tear, referral should be offered. The distance from the anus to the tear is critical because the peritoneal cavity extends to within 15 to 20 cm of the anus in mature horses. The average distance from the anus to the rectal tear is 30 to 40 cm, which is well within the abdominal cavity. At this location the tear is actually within the small colon. Rectal tears are most commonly located dorsally, possibly because the mesenteric vasculature penetrates the intestinal musculature at this location, and the small colon deflects ventrally from the rectum.

## CLIENT COMMUNICATION

Once the extent of the tear has been determined, an initial conversation with the owner should include details of the problem and an explanation of what must be done to treat the horse. This step is particularly critical for severe (grades 3 and 4) rectal tears. The most difficult component of this conversation is informing clients that they are financially responsible for medical and surgical treatment of the rectal tear. An admission of guilt or an implication that the veterinarian will take responsibility for payment of medical fees should not be made, and the liability insurance agent should be informed of the circumstances as soon as possible. Furthermore, it should not be implied that the insurance company would cover medical costs because this decision centers on whether a legal suit is filed and whether negligence has occurred. In the large majority of cases, negligence is not proven. The veterinarian at the referral hospital may instigate much of the preliminary conversation with the client. The referral veterinarian should explain possible therapy options, cost, and responsibility for medical fees.

## EMERGENCY TREATMENT FOR RECTAL TEARS

Fecal material should be evacuated completely from the rectum. Epidural anesthesia may aid this procedure in cases in which concern exists about the horse straining. Grade 1 rectal tears usually resolve with conservative medical treatment, including administration of broad-spectrum antibiotics (e.g., trimethoprim-sulfonamide, 20 mg/kg PO q12h) and flunixin meglumine (1.1 mg/kg IV or PO q12h). A laxative diet such as bran mash should be provided, and the horse should be closely monitored for signs of tear progression, including signs of colic or endotoxemia. If the tear is grade 3 or 4 and treatment is going to be pursued, the horse should be given broad-spectrum intravenous (IV) anti-biotics (penicillin [22,000 IU/kg IV] and gentamicin [4 mg/kg IV]), flunixin meglumine, and tetanus toxoid and should be referred as rapidly as possible. The total length of time from the onset of the rectal tear to arrival at the referral hospital should be less than 6 hours to maximize the horse's chances of survival.

Some debate exists regarding whether the rectum should be packed before referral to prevent feces from enlarging the rectal tear. This procedure involves packing of the rectum with stockinette filled with gauze or rolled cotton from the region cranial to the tear back to the anus. Epidural anesthesia is required for this procedure. Because most tears are more than 30 cm proximal to the anus, this procedure may take considerable time. Therefore rapid transfer of the horse may be advantageous if the referral hospital is within a reasonable distance (3- to 4-hour trailer ride), reserving rectal packing for those horses that have extensive travel time or in cases in which the owner needs considerable time to make a decision.

Although grade 4 tears are almost always fatal, these horses often should be referred for a second opinion to confirm the diagnosis and provide therapy if appropriate. Some grade 4 rectal tears within 15 cm of the anus are not intraabdominal and can be successfully managed. For

horses that unquestionably have a grade 4 rectal tear within the abdominal cavity, euthanasia is indicated. Abdominocentesis can be very helpful in horses with grade 3 or 4 rectal tears to document the degree of abdominal inflammation and contamination. Expected findings are cloudy fluid, elevated protein ( $>2.5$  g/dl), elevated cell count ( $>10,000$  nucleated cells/ $\mu$ l), and intracellular or extracellular bacteria, depending on the grade and extent of the tear. These changes usually begin to occur within 1 hour of the inciting injury.

## TREATMENT OPTIONS FOR SEVERE RECTAL TEARS

Some knowledge of the various treatment options for severe rectal tears is helpful to discuss options with the owner before referral. One of the simplest approaches for management of rectal tears is to evacuate the rectum every 1 to 2 hours for 72 hours, thereby ensuring that feces does not pack within the rectal defect. Fecal packing tends to enlarge the tear and may lead to progression from a grade 3 rectal tear to a grade 4 tear. Frequent rectal evacuation is best reserved for horses that have small rectal tears ( $<10$  cm in diameter). An alternate but similar technique is to take the horse to surgery, perform large colon and small colon enterotomies to empty the bowel, and withhold feed in the 1-week postoperative period. After the first week the horse should eat a low-residue feed.

For extensive grade 3 rectal tears, alternative surgical techniques usually are required. Direct suturing of the tear either via the rectum or via laparotomy approach to the small colon is usually hampered by the location of the tear, which is typically located out of reach with either approach. However, suturing can sometimes be completed with tears close to the anus. Furthermore, partial suturing of large rectal tears can be used in combination with other treatments, such as fecal diversion via colostomy or rectal liner, to hasten healing of the tear. Rectal liners consist of plastic rectal sleeves with the hand cut off and glued to porcine prolapse rings. The procedure requires a midline laparotomy so that a surgeon can assist via the abdomen while the ring is inserted per rectum proximal to the tear. The surgeon places an encircling suture around the ring, followed by an inverting suture pattern to prevent catastrophic rupture when the circumferential suture and sleeve are sloughed. The major complication with this technique is premature loss of the liner (usually within 10-14 days), whereas the tear may take up to 21 days to heal by second intention.

For loop colostomy the small colon is exteriorized through an incision in the left flank, preferably with the horse standing (Figure 3.20-2). This procedure can be accomplished with the horse in lateral recumbency, but the colostomy usually tears during recovery as the flank muscles contract. If the horse requires abdominal exploratory surgery for evaluation of colic (often the initial reason that rectal palpation was performed), consideration should be given to performance of the exploratory first, recovery of the horse from anesthesia, and performance of the colostomy with the horse standing. Postoperatively the



**Figure 3.20-2** Diverting loop colostomy in a horse with a grade 3 rectal tear. The proximal small colon lumen (*right arrow*) is ventral to the distal small colon lumen (*left arrow*) to facilitate defecation. Note the presence of petroleum jelly on the colonic mucosa to prevent mucosal sloughing.

tear is observed and lavaged with the assistance of an endoscope. The distal segment of the colon may be flushed per rectum to remove accumulated mucus. Colostomy complications include peristomal hernia formation, self-mutilation of the stoma, sloughing of the stomal mucosa, and atrophy of the distal colon. Once the tear has granulated (usually within 14-21 days), the colostomy is resected. Although considerable success has been reported with this technique, the expense and morbidity rates are high. Other treatment options such as laparoscopy also are being investigated.

## SUMMARY

Although the thought of injuring a horse's rectum during palpation is unpleasant, a veterinarian who is knowledgeable on what to do usually can avoid claims of negligence and successfully treat the horse. Rapid, decisive decision making is required, together with clear-cut communications with all those involved. The referring veterinarian should seek advice and support from the referral practice, which in turn should reinforce the concept that rectal tears are an unfortunate but sometimes unavoidable consequence of equine practice. The referral hospital must provide a definitive diagnosis and give the owner a range of treatment options according to the nature of the rectal tear.

## Supplemental Readings

- Baird AN, Freeman DE: Management of rectal tears. *Vet Clin North Am Equine Pract* 1997; 13:377-392.
- Blikslager AT, Bristol DG, Bowman KF et al: Loop colostomy for treatment of grade-3 rectal tears in horses: seven cases (1983-1994). *J Am Vet Med Assoc* 1995; 207:1201-1205.
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- Mair TS: The medical management of eight horses with grade 3 rectal tears. *Equine Vet J* 2000; 32(Suppl):104-107.
- Taylor TS, Watkins JP, Schumacher J: Temporary indwelling rectal liner for use in horses with rectal tears. *J Am Vet Med Assoc* 1987; 191:677-680.

# CHAPTER 3.21

## Peritonitis

JAN F. HAWKINS  
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**P**eritonitis is an inflammatory condition of the mesothelial lining of the abdominal cavity. Peritonitis can be septic or nonseptic in origin. However, in horses it is usually secondary to infectious, traumatic, chemical, or parasitic peritoneal insults and can be a major complication of abdominal surgery. The reported mortality rates for peritonitis in the horse range from 30% to 67%. However, mortality rates are dependent on the cause. For example, the mortality rate for peritonitis after abdominal surgery is 56% and for peritonitis not associated with abdominal surgery or intestinal rupture 43%.

The etiology, incidence, and pathogenesis of equine peritonitis have been reviewed extensively in previous editions of *Current Therapy in Equine Medicine*. This chapter emphasizes the clinical signs, diagnostic procedures, and treatment for horses with septic peritonitis.

## CLINICAL SIGNS

The most common presenting clinical sign of septic peritonitis is pyrexia ( $>39.5^{\circ}\text{C}$  [ $101.5^{\circ}\text{F}$ ]). Other presenting clinical signs include depression, anorexia, diarrhea, and



**Figure 3.20-2** Diverting loop colostomy in a horse with a grade 3 rectal tear. The proximal small colon lumen (*right arrow*) is ventral to the distal small colon lumen (*left arrow*) to facilitate defecation. Note the presence of petroleum jelly on the colonic mucosa to prevent mucosal sloughing.

tear is observed and lavaged with the assistance of an endoscope. The distal segment of the colon may be flushed per rectum to remove accumulated mucus. Colostomy complications include peristomal hernia formation, self-mutilation of the stoma, sloughing of the stomal mucosa, and atrophy of the distal colon. Once the tear has granulated (usually within 14-21 days), the colostomy is resected. Although considerable success has been reported with this technique, the expense and morbidity rates are high. Other treatment options such as laparoscopy also are being investigated.

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## CLINICAL SIGNS

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mild to moderate signs of abdominal pain. Affected horses often are dehydrated with the level of dehydration ranging from 8% to 10%. A packed cell volume (PCV) exceeding 40% is not unusual. Mucous membrane color is usually red or hyperemic and a toxic gum line may be observed. Capillary refill time is elevated to greater than 2 seconds. Tachycardia frequently is present and is associated with dehydration and endotoxemia. Auscultation of the abdominal cavity reveals decreased intestinal sounds indicative of ileus.

## DIAGNOSTIC PROCEDURES

The following diagnostic procedures are recommended for all suspected cases of septic peritonitis: complete blood count (CBC), fibrinogen concentration, biochemical profile, serum electrolytes, abdominocentesis, peritoneal fluid microbial culture and cytology, abdominal palpation per rectum, and transabdominal or transrectal ultrasound.

### Complete Blood Count

Abnormal CBC results include leukocytosis ( $>12,000$  nucleated cells/ $\mu\text{l}$ ), hyperfibrinogenemia ( $>400$  mg/dl), and polycythemia secondary to dehydration, hypoproteinemia secondary to protein exudation into the peritoneal cavity or hyperproteinemia secondary to dehydration. However, in chronic cases of peritonitis the nucleated cell count may be normal or only mildly elevated above normal. In acute cases of septic peritonitis horses are frequently leukopenic ( $>4000$  nucleated cells/ $\mu\text{l}$ ) secondary to accumulation of leukocytes in the abdominal cavity. Likewise in acute cases of septic peritonitis the serum total protein concentration is frequently below the normal reference range. This occurs secondary to protein exudation, particularly fibrinogen exudation, into the peritoneal cavity. Hyperfibrinogenemia ( $>500$  mg/dl) commonly is associated with an intraabdominal abscess.

### Biochemical Profile and Electrolyte Abnormalities

The most common biochemical profile abnormalities associated with septic peritonitis are elevations in blood urea nitrogen (BUN) and creatinine. Azotemia is typically prerenal in origin. Because of the large volumes of fluid exudation into the peritoneal cavity dehydration is not uncommon. The exudation of fluid leads to decreased glomerular filtration rate and prerenal azotemia. Serum electrolyte disturbances include hypokalemia, hyponatremia, hypochloremia, and hypocalcemia. Hypokalemia occurs secondary to anorexia and decreased roughage intake, and gastrointestinal losses associated with diarrhea and extracellular fluid shifts are associated with dehydration. Hyponatremia and hypochloremia can be associated with gastrointestinal losses and dehydration. Hypocalcemia frequently is observed secondary to decreased roughage intake and acid-base disturbances. The most common acid-base disturbance is metabolic acidosis.

### Abdominocentesis

Abdominocentesis is technically not demanding and is indicated in all suspected cases of septic peritonitis. Ab-

dominocentesis must be performed with care because the risk for enterocentesis does exist and is not an infrequent occurrence. Two methods of abdominocentesis are described. The first method involves the use of an 18-gauge 1½- to 3-inch needle, and the second method involves the use of canine urinary catheter. Because of the effusive nature of peritonitis, peritoneal fluid is generally easy to obtain. To perform abdominocentesis a 5-cm  $\times$  5-cm area of hair should be clipped from the ventral abdomen. The preferred location is approximately 10 cm caudal to the xiphoid and 10 cm to the right of the ventral midline. In general the most dependent aspect of the abdomen is chosen. The area right of midline is chosen to prevent penetration of the spleen, which rests on the ventral abdominal midline or just towards the left of midline.

After aseptic preparation, the needle is inserted into the abdomen. This author finds it helpful to rest the wrist on the ventral abdominal wall adjacent to the puncture site. This steadies the needle and prevents peritoneal penetration with a single insertion of the needle. Once the needle penetrates the skin and subcutaneous tissue the needle is advanced slowly until a "pop" is felt. This indicates that the peritoneum has been penetrated.

In horses with an excessive amount of retroperitoneal fat a 3-inch spinal needle may be required to obtain peritoneal fluid. Peritoneal fluid should be collected into an ethylenediaminetetraacetic acid (EDTA) tube for cytologic analysis. If peritoneal fluid does not readily exit the needle, additional needles can be placed adjacent to the first. This is done to sample "pockets" of peritoneal fluid created by the location of the intestinal viscera. If blood is obtained, the needle is withdrawn and a second site is chosen.

Obtaining blood usually means that the spleen has been penetrated. Spleen penetration can be determined by measuring PCV and total protein concentration on the collected fluid. Splenic blood has a similar if not higher value when compared with the peripheral blood sample. If blood is obtained from multiple sites, then hemoperitoneum must be considered. If intestinal contents are obtained the needle is withdrawn and a second site is chosen. In most cases of enterocentesis, no ill effects are observed. However, this author has observed puncture sites during surgical exploration that were leaking intestinal contents into the peritoneal cavity. If enterocentesis does occur the veterinarian should warn the owner about the potential risks of iatrogenic peritonitis after the procedure.

If peritoneal fluid cannot be obtained with percutaneous needle placement, a sterile canine urinary catheter can be used. These catheters are constructed of metal and have a blunt, curved end. The preparation and site location of abdominocentesis using this type of catheter is the same as described previously. However, the two techniques differ. The skin, subcutaneous tissues, and external rectal sheath are desensitized with 3-ml of local anesthetic. To facilitate penetration of the abdominal wall with the catheter a stab incision is made into the skin and external rectus sheath with a number 15-scalpel blade. The incision must be wide enough to accommodate the catheter. Insufficient size of the initial incision requires use of a significant amount of force to penetrate the external rectus sheath. If a sudden thrusting of the catheter into the peritoneal cavity occurs,

iatrogenic penetration of abdominal viscera can occur. To prevent blood contamination of the peritoneal fluid sample, gauze sponges are wrapped around the catheter to absorb blood originating from the body wall stab incision. The catheter is inserted into the abdomen. A small amount of resistance is not an unexpected finding with this technique. Once the peritoneal cavity has been entered, peritoneal fluid collection is performed as described previously. It may be necessary to move the catheter to multiple areas to enter a "pocket" of peritoneal fluid.

### Microbial Culture of Peritoneal Fluid

Microbial culture of the peritoneal fluid should be performed in all cases of suspected septic peritonitis. Microbial culture results guide antimicrobial therapy once sensitivity against the causative agent is obtained. Peritoneal fluid can be placed in a red top collection tube for microbial culture or commercially available culture medium devices. This author prefers to use a commercially available culture 5-ml vial named Port-A-Cul (Becton and Dickinson, Sparks, Md.). The Port-A-Cul is suitable for culture for aerobic and anaerobic bacteria. Both aerobic and anaerobic cultures should be performed. Positive anaerobic cultures are not unusual. To successfully isolate anaerobes, culture tubes or vials must not be refrigerated. Culture tubes should be placed at room temperature or in an incubator until microbiologic cultures can be performed. Peritoneal fluid is collected as described for abdominocentesis. Peritoneal fluid is collected using aseptic technique. This author uses a 12-ml syringe to collect the fluid as it drips from the needle or canine urinary catheter. The contents of the syringe are then injected into the culture tube.

### Peritoneal Fluid Cytology

Cytologic analysis of peritoneal fluid is an effective way to determine the presence of bacteria and degenerative neutrophils in the peritoneal fluid. Gross analysis of the peritoneal fluid always is indicated. Normal peritoneal fluid is clear and yellow tinged. Abnormal peritoneal fluid associated with peritonitis is usually dark yellow or orange and appears turbid. In cases of intestinal rupture feed material may be present within the peritoneal fluid. Peritonitis associated with ischemic intestine often has a serosanguineous or blackish-brown appearance. Even if laboratory analysis of peritoneal fluid is not immediately available, a total protein concentration can be obtained with a refractometer. Likewise Diff-Quik stain (Dade Behring, Inc., Deerfield, Ill.) can be used to stain a smear of peritoneal fluid. The normal nucleated cell count for normal horses should be less than 5000 nucleated cell/ $\mu$ l and the normal total protein concentration should be less than 2.5 g/dl. Cytologic abnormalities associated with peritonitis include degenerate, toxic neutrophils and intracellular or extracellular bacteria. The presence of free or intracellular bacteria is associated with a guarded to poor prognosis.

### Abdominal Palpation per Rectum

Abdominal palpation per rectum is recommended for all cases of suspected septic peritonitis. Rectal examination

in suspected cases of peritonitis should include careful palpation of the intestinal serosal surfaces and evaluation of the dorsal mesentery. Horses with septic peritonitis secondary to intestinal rupture frequently have palpable crepitus secondary to intraabdominal gas accumulation and contamination of the serosal surfaces with feed material. In horses with an abdominal abscess a mass may be palpable within the intestinal mesentery or within the mesocolon of the large colon. Adhesion formation between loops of intestine also may be palpable. Finally distended loops of small or large intestine may be felt when adhesions have formed around intestinal foreign bodies or sites of focal perforations or when intestinal ileus is present.

### Abdominal Ultrasound Examination

Transabdominal ultrasound can be helpful in determining sites for abdominocentesis when peritoneal fluid is not immediately obtained with traditional methods of collection. Focal "pockets" of fluid can be identified with transabdominal, ventral midline examination, and sampled as previously described. If transabdominal ultrasound is not available, transrectal ultrasound with a reproduction probe can be used to image palpable masses or intraabdominal abscesses. Normal peritoneal fluid is typically hypoechoic but in cases of septic peritonitis peritoneal fluid usually appears hyperechoic and turbid. Fibrin tags or strands also may be observed within the peritoneal fluid or covering the serosal surfaces. In some instances thickened intestinal surfaces may be imaged. Intraabdominal masses, which could include neoplasia or intraabdominal abscesses, also may be imaged. Depending on the location of these masses ultrasound guided aspirates can be obtained. Samples can then be obtained for microbial culture or histopathology.

## TREATMENT

### Intestinal Rupture

In cases of intestinal rupture that are documented by abdominocentesis, abdominal palpation per rectum, and/or exploratory celiotomy, the only viable treatment in most instances is euthanasia. However, horses that have focal perforations surrounded with adhesions can be managed successfully with abdominal surgery. This author recommends against making a decision for euthanasia based on abdominocentesis only because the veterinarian may have performed repeated enterocentesis and the horse may not have intestinal rupture. When the veterinarian cannot prove that rupture has occurred, an exploratory celiotomy is indicated to prove or refute the diagnosis of intestinal rupture.

### Treatment of Horses without Intestinal Rupture

Treatment of septic peritonitis not associated with intestinal rupture includes the administration of antimicrobials and antiinflammatories, correction of dehydration, abdominal lavage, and abdominal surgery.

### **Antimicrobial and Antiinflammatory Therapy**

Antimicrobial therapy should be guided by peritoneal fluid microbial culture results. Pending the results of microbial culture, empiric treatment with broad-spectrum antimicrobials should be performed. This author recommends horses with suspected septic peritonitis be treated with intravenous (IV) antimicrobials for aerobic bacteria and per os for anaerobic bacteria. IV administration obtains immediate blood levels and unlike the oral and intramuscular (IM) routes, absorption is ensured and predictable. The best combinations of antimicrobials include a  $\beta$ -lactam, an aminoglycoside, and an antimicrobial effective against anaerobic bacteria. The most common  $\beta$ -lactam antimicrobials used are potassium penicillin G (22,000 IU/kg IV q6h) and ceftiofur sodium (2.2 mg/kg IV q12-24h). Aminoglycosides act synergistically with  $\beta$ -lactams such as penicillin G. The most common aminoglycoside used is gentamicin sulfate (6.6 mg/kg IV q24h). In selected cases of septic peritonitis in which gentamicin sulfate is not effective, amikacin sulfate can be used. This author reserves amikacin sulfate administration for animals in which the treatment of peritonitis is nonresponsive to gentamicin therapy and in situations in which owners can afford this expensive agent.

Penicillin G and metronidazole provide anaerobic bacterial coverage. Penicillin G is effective against many anaerobes with the exception of *Bacteroides fragilis*. To provide coverage against this bacterial species and other anaerobes, metronidazole can be used. The recommended dosage of metronidazole is 15 mg/kg by mouth every 6 hours or 20 mg/kg by mouth every 8 hours or 30 mg/kg by mouth every 12 hours. Obviously once the results of the peritoneal fluid microbial culture have been obtained, antimicrobials are chosen based on the sensitivity pattern against the isolated organism. The most common antiinflammatory agent used for treatment of endotoxemia associated with equine septic peritonitis is flunixin meglumine (1.1 mg/kg IV q12h).

An additional antiinflammatory often administered in cases of septic peritonitis is dimethyl sulfoxide (DMSO). DMSO (500 ml of a 90% solution added to a minimum of 5 L of balanced polyionic fluid) has antiinflammatory properties, which may be helpful in the management of equine septic peritonitis. Hyperimmune plasma containing antientotoxigenic antibodies can be used. Typically 1 to 2 L of hyperimmune plasma are administered. Hyperimmune plasma supplies antientotoxin antibodies and replenishes plasma proteins, which appear to improve the clinical signs associated with endotoxemia.

### **Correction of Dehydration**

Hydration deficits are corrected via IV fluid administration. However, in instances in which the gastrointestinal tract is functioning normally, water-containing electrolytes can be administered via nasogastric tube. To treat dehydration, large-bore (10- to 14-gauge) IV catheters should be inserted into one or both jugular veins. In horses with a PCV greater than 45% a bolus of hypertonic (7.2%) saline solution intravenously at a dosage of 4 ml/kg is administered. At this dosage, 1.8 L of hypertonic solution is administered to a 450-kg horse. To maximize the effectiveness of hypertonic saline, immediately after its ad-

ministration large volumes of balanced polyionic fluids should be administered intravenously. The rate of fluid administration should be at least twice (2-4 L/hr) the maintenance fluid requirement (1-2 L/hr) until the hydration deficit has been corrected. To correct deficiencies of potassium and calcium these electrolytes are added to the IV fluids. Potassium is administered at a dosage of 20 to 40 mEq/L of balanced polyionic fluid. Even at rapid rates of fluid administration this author has not experienced any deleterious side effects associated with potassium administration. Calcium borogluconate should be administered at a dosage of 500 ml of a 23% solution added to a minimum of 5 L of balanced polyionic fluid.

### **Abdominal Lavage**

Percutaneous abdominal lavage is a controversial treatment of septic peritonitis in horses. This author believes abdominal lavage can be an effective treatment and should be considered in all cases of septic peritonitis managed medically. Abdominal lavage typically is performed with the horse standing. A 28 Fr Argyle Trocar Thoracic Catheter (28 Fr  $\times$  16 inches, Tyco Healthcare Group, Mansfield, Mass.) is placed into the most dependent portion of the abdomen. The tube is inserted to the right of midline to avoid the spleen. After sedation with IV xylazine or detomidine hydrochloride, the skin, subcutaneous tissue, and external rectus sheath are locally infiltrated with 3 to 5 ml of local anesthetic. A stab incision is made through the skin, subcutaneous tissue and external rectus sheath with a number 15-scalpel blade. The incision in the external rectal sheath must be large enough to accommodate the diameter of the chest tube inserted into the abdominal cavity. If the incision is not large enough, the operator has to use a tremendous amount of pressure to penetrate the external rectus sheath. The end result can be a sudden penetration of the body wall and iatrogenic perforation of the cecum or large colon. The risk of iatrogenic perforation is thus minimized with a liberal incision and careful penetration of the abdominal wall.

The chest tube is then inserted into the abdominal cavity. Once the trocar located within the catheter has penetrated the abdominal wall, the trocar is removed and the catheter is inserted into the abdominal cavity. The tube is then secured to the abdominal wall with a purse-string suture and further stabilized with a Chinese finger trap pattern around the tube. Once inserted and secured, free peritoneal fluid is drained from the abdomen. Balanced polyionic fluids (e.g., lactated Ringer's or 0.9% sodium chloride) are then allowed to flow under the influence of gravity into the abdominal cavity. This author uses an arthroscopic fluid delivery system (Two Lead Arthroscopic Irrigation Set, Baxter Healthcare, Deerfield, Ill.) to deliver the lavage fluid.

The key to a successful abdominal lavage in the standing horse is to instill a large volume of lavage fluid into the abdomen. A large volume of fluid should be administered to ensure the majority of the intestinal viscera and peritoneal surfaces come in contact with the lavage fluid. At lower volumes only the most ventral portion of the abdominal cavity come in contact with the lavage fluid. This author recommends a minimum of 20 L of fluid be instilled into the abdomen at one time. Horses may experi-

ence mild abdominal discomfort after instillation of this much fluid. If the horse becomes too uncomfortable, fluid can be allowed to drain back out of the catheter. If possible the horse is walked after instillation of lavage fluid to encourage the bathing of the intestine with as much fluid as possible. After a short period of walking the horse is again restrained and the fluid is drained from the abdomen.

Some fluid may remain in the abdomen. In this author's experience, the remaining fluid is absorbed from the peritoneal surfaces and causes few, if any, problems. Once abdominal lavage has been completed, a sterile syringe is placed in the open end of the abdominal drain. This author does not routinely secure the abdominal drain with a bandage. This author has not experienced problems with ascending infection with indwelling abdominal drains of several days' duration.

The abdominal lavage procedure can be performed once or twice daily. This author generally performs lavage once daily for 3 to 5 days after initial placement of the lavage catheter. The decision for drain removal is based on improvement in clinical signs and return of the abdominal fluid parameters towards normal levels. If the drain is left for longer than this, it frequently becomes covered with omentum. Covering the catheter with omentum allows fluid to be instilled into the abdomen but prevents easy fluid drainage from the abdomen. The abdominal drain is removed by removing the purse string suture and the catheter is withdrawn from the abdomen. The veterinarian should be aware that if omentum has attached itself to the catheter, it may be pulled from the abdomen when the catheter is removed. If this occurs the exposed omentum should be ligated with suture material and removed. The omental stump is returned to the abdomen and the skin is sutured with nonabsorbable suture material.

### **Surgical Treatment of Septic Peritonitis**

Horses affected by septic peritonitis often require surgical exploration of the abdominal cavity to determine the source of peritonitis. If a source of peritonitis cannot be determined after the diagnostic procedures described above, surgical exploration is indicated. Exploratory celiotomy allows the surgeon to determine the source of peritonitis and correct it when possible; it also facilitates abdominal lavage.

A description of surgical procedures to correct causes of septic peritonitis is beyond the scope of this chapter. Individuals interested in surgical treatment of septic peritonitis should review surgical textbooks pertaining to abdominal surgery in the horse.

Abdominal lavage via ventral midline celiotomy is the best way to lavage the serosal surfaces of horses with septic peritonitis. In general lavage fluid is instilled into the abdomen until the effluent is clear and no longer cloudy. To ensure this, simultaneous lavage and suction are performed. It frequently requires a minimum of 20 to 30 L of fluid to accomplish this. The same type of fluid delivery system described under the section for abdominal lavage is used. Once the abdominal lavage has been completed, the surgeon can decide for or against further abdominal lavage with indwelling abdominal drains. This decision is made based on what the source of peritonitis was and

whether continued abdominal contamination is likely. The best example is continued drainage from an abdominal abscess after intraabdominal decompression.

### **Monitoring the Clinical Response to Treatment**

#### ***Antimicrobial and Antiinflammatory Therapy***

If a positive microbial culture was obtained from the peritoneal fluid the horse is treated for a minimum of 2 weeks with antimicrobials based on the sensitivity results. It is not unusual to treat affected horses for at least 4 to 6 weeks with antimicrobials to ensure complete remission of septic peritonitis. Horses with intraabdominal abscess formation may require treatment for up to 4 months to resolve abdominal abscessation. If possible, the resolution of abdominal abscesses should be monitored with transabdominal or transrectal ultrasound.

The decision for discontinuation of antimicrobials is made based on the resolution of pyrexia, dehydration, and anorexia associated with peritonitis. Abdominocentesis is used to evaluate the peritoneal response to inflammation. The nucleated cell count and total protein concentration should dramatically decrease with appropriate treatment. However, it may take 4 to 6 weeks for these parameters to return to normal. Antiinflammatory therapy is continued for as long as the horse is febrile, endotoxic, or anorexic. In general nonsteroidal antiinflammatory drug (NSAID) therapy is administered for a minimum of 5 to 7 days. NSAID therapy must be discontinued to accurately assess the presence or absence of pyrexia.

#### ***Dehydration***

Clinical findings and serial monitoring of the PCV and total protein concentration assess dehydration. IV fluids are discontinued when the horse is able to maintain its own hydration with oral intake of water or oral electrolytes. The rate of fluid administration is decreased gradually until a normal amount of water and feed is being consumed. However, some horses do not ingest a normal amount of water until IV fluid therapy has been discontinued. Deficits in potassium and calcium generally are corrected once the horse returns to a normal level of roughage intake.

#### ***Abdominal Lavage***

Abdominal lavage is performed for a minimum of 3 to 5 days after placement of the abdominal drain. The decision for drain removal is based on the horse's clinical signs and serial peritoneal fluid analysis. Reductions in nucleated cell count and total protein concentration are indicative of successful treatment. Peritoneal fluid collection is straightforward because the peritoneal fluid can be collected from the indwelling drain. The peritoneal fluid must be collected before abdominal lavage. If sample collection is performed after abdominal lavage the nucleated cell count and total protein concentration will be diluted and inaccurate.

### **PROGNOSIS**

The prognosis for septic peritonitis depends on the clinical response to treatment and whether the horse devel-

ops intraabdominal adhesions or continued abscessation. Horses that do not respond to antimicrobial therapy and abdominal lavage have a poor prognosis. Horses with bacteria observed on cytologic examination of the peritoneal fluid also have a guarded to poor prognosis. Horses successfully treated for peritonitis may continue to lead productive lives. However, even if horses are treated successfully for septic peritonitis, they may develop intraabdominal adhesions, which can cause recurrent colic, poor weight gain, or poor performance.

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## CHAPTER 3.22

# Intestinal Tapeworm Infestation

CHRISTOPHER J. PROUDMAN

*Leahurst, Neston, Wirral, United Kingdom*

### ETIOLOGY OF TAPEWORM-ASSOCIATED INTESTINAL DISEASE

#### Pathology of Tapeworm Infection

The common intestinal tapeworm (*Anoplocephala perfoliata*) attaches to the intestinal mucosa at the ileocecal junction. A number of postmortem studies have identified ulceration, edema, and inflammation of the mucosa at this site in the presence of large numbers of tapeworms. The extent of the pathologic changes is proportional to the number of parasites attached. Small numbers of tapeworms cause relatively little damage. However, large numbers, all attached to a small area of mucosa around the junction, can cause massive ulceration and even rupture of the intestine.

#### Epidemiology of Tapeworm Infection

Studies from around the world have reported prevalence of *A. perfoliata* ranging from 14% to 81%. These studies indicate that countries with a temperate climate are likely to have a higher prevalence of this parasite and countries with a hot, arid climate have lower prevalence. This trend may reflect the relative abundance of the intermediate host of the parasite, the oribatid mite.

As with all intestinal parasite infections, the equine tapeworm is distributed among its host population in a nonrandom manner. Certain animals are predisposed to developing high infection intensities. This results in 80% of the parasites residing in 20% of the hosts. Such a distribution has implications for disease control highlighted later in this chapter. An age-intensity study demonstrated that young horses (between 6 months and 2 years old) are most likely to harbor the highest tapeworm burdens.

For many years, the equine tapeworm was thought to

be relatively harmless. However, a large number of case series and individual case reports made a circumstantial association between the presence of large numbers of tapeworms and certain types of colic arising from problems at the ileocecal junction. This situation has been investigated epidemiologically and two case-control studies have identified tapeworm infection as a risk factor for spasmodic colic and ileal impaction colic. Furthermore, the risk of tapeworm-associated colic is proportional to infection intensity. This finding is consistent with the observation that ileocecal pathology is proportional to infection intensity.

### INVESTIGATION OF TAPEWORM INFECTION

Unlike infection with some intestinal helminths, tapeworm infection leads to few external signs of disease. In many cases, the first indication of tapeworm infection is an episode of colic in the infected animal. Weight loss, ill thrift, changes in hair coat, and diarrhea are not indicative of tapeworm infection.

#### Coprologic Diagnosis

Fecal flotation methods have been described for the detection of tapeworm eggs in the feces of infected horses. Although these tests are inexpensive and demand no sophisticated equipment, they are time consuming and messy and lack sensitivity. Validation studies of various coprologic methods have reported sensitivities of 11% to 61%. Processing large numbers of samples using coprologic methods is difficult. An important feature of all the techniques described is the use of a high specific gravity flotation solution. A saturated sodium chloride solution

ops intraabdominal adhesions or continued abscessation. Horses that do not respond to antimicrobial therapy and abdominal lavage have a poor prognosis. Horses with bacteria observed on cytologic examination of the peritoneal fluid also have a guarded to poor prognosis. Horses successfully treated for peritonitis may continue to lead productive lives. However, even if horses are treated successfully for septic peritonitis, they may develop intraabdominal adhesions, which can cause recurrent colic, poor weight gain, or poor performance.

### Supplemental Readings

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For many years, the equine tapeworm was thought to

be relatively harmless. However, a large number of case series and individual case reports made a circumstantial association between the presence of large numbers of tapeworms and certain types of colic arising from problems at the ileocecal junction. This situation has been investigated epidemiologically and two case-control studies have identified tapeworm infection as a risk factor for spasmodic colic and ileal impaction colic. Furthermore, the risk of tapeworm-associated colic is proportional to infection intensity. This finding is consistent with the observation that ileocecal pathology is proportional to infection intensity.

### INVESTIGATION OF TAPEWORM INFECTION

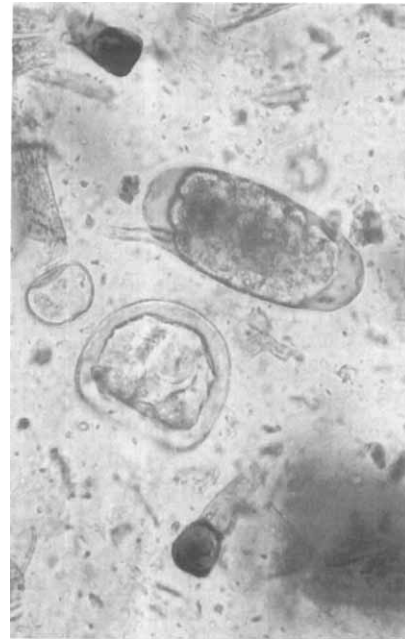
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**BOX 3.22-1****Centrifugation/Flotation Method for the Coprologic Diagnosis of Tapeworm Infection**

1. Mix approximately 30 g feces with 5 to 10 ml tapwater until the fecal material becomes pasty in consistency.
2. Strain the fecal slurry through a coarse sieve, collecting the liquid in two 15ml centrifuge tubes.
3. Spin both tubes at approximately 1200 g for 10 minutes.
4. Discard the supernatant and resuspend the fecal plug in tapwater.
5. Repeat step 3, discard the supernatant but now resuspend the fecal plug in saturated sugar solution (450 g sucrose in 350 ml warm water, stir until dissolved).
6. Repeat step 3, and after spinning top-up to the brim with saturated sucrose solution, place a cover slip on top of each centrifuge tube and allow to stand for 1 to 2 hours.
7. Remove coverslips, place on microscope slide, and scan at  $\times 10$  for cestode eggs. *Anoplocephala perfoliata* eggs have a characteristic D shape and a thick, refractile shell containing a circular onchosphere and supporting pyriform apparatus (see Fig. 3.22-1).



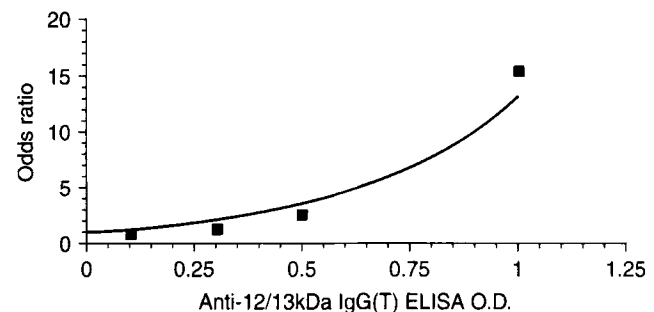
**Figure 3.22-1** Microscopic appearance of a tapeworm egg (lower left of center) adjacent to a strongyle egg. Note the thick, refractile shell of the tapeworm egg and its internal structure.

(as used for a McMaster flotation for strongyle eggs) does not float tapeworm eggs. A saturated sucrose solution is the simplest to prepare and the least expensive. A protocol for the detection of tapeworm eggs from feces is given in Box 3.22-1. Tapeworm eggs have a characteristic appearance under the microscope (Figure 3.22-1). They are approximately the same size as strongyle eggs but are usually D-shaped, with a thick, refractile shell. Inside the egg, a circular onchosphere is apparent with supporting pyriform apparatus. This has the appearance of the "World Cup" soccer trophy.

**Serologic Diagnosis**

Tapeworm infection has been demonstrated to stimulate an antibody response in infected horses. In particular, an IgG(T) response to an excretory/secretory antigen has been measured. This antibody response forms the basis of a diagnostic tapeworm antibody enzyme-linked immunosorbent assay (ELISA). Test results from the ELISA correlate with infection intensity. This information is important clinically because the risk of tapeworm-associated colic is known to be proportional to infection intensity. The relationship between the risk of spasmodic colic and tapeworm ELISA optical density was explored in a case-control study and Figure 3.22-2 demonstrates the form of this relationship.

A number of horses with high tapeworm antibody ELISA results have been retested after treatment. The fall in antibody response depends upon the dynamics of equine IgG(T) and takes 12 to 16 weeks to decline to a "normal" level. If exposed to reinfection, the decline in tapeworm-specific IgG(T) may be only partial.



**Figure 3.22-2** Graph illustrating the relationship between tapeworm infection intensity (as measured by the tapeworm antibody enzyme-linked immunosorbent assay [ELISA]) and the risk of spasmodic colic. Relationship described by conditional logistic regression model using results from a matched case-control study.

**TREATMENT**

The benzimidazoles, ivermectin and moxidectin, have no efficacy against tapeworms. Pyrantel in its various formulations is effective in fighting *A. perfoliata*. In North America pyrantel pamoate is available and removes up to 87% of *A. perfoliata* at a dose of 6.6 mg/kg. In the United Kingdom pyrantel embonate formulations are available with a label claim for the control of *A. perfoliata* when used at a dose of 38 mg/kg (efficacy is reported to be 93%). The nematocidal dose (19 mg/kg) also has moderate efficacy against tapeworms. Daily administration of pyrantel tartrate, at a dose rate of 2.6 mg/kg, probably also is effective at eliminating tapeworms from infected horses. However, efficacy studies of this drug regimen have been completed on only small numbers of horses.

Praziquantel is also highly effective at killing *A. perfoliata*. A combination anthelmintic preparation containing ivermectin and praziquantel is available in some countries. This product is formulated to kill both strongyles and tapeworms. At present, no preparation exists of praziquantel alone, licensed for use in the horse. However, administration of the injectable formulation of praziquantel, licensed for use in dogs and cats, by stomach tube or intraorally, is both safe and effective against equine tapeworms. A dose rate of 1 mg/kg reportedly removes 98% of tapeworms and a dose rate of 0.5 mg/kg removes an average of 85% of tapeworms.

Occasionally, horse owners report that their animal is infected with tapeworms, which are "resistant to pyrantel." The owners usually have observed tapeworm segments in the feces of their horses that persist after pyrantel treatment. The presence of barrel-shape segments in the feces is highly suggestive of infection with *Anoplocephaloides mamillana* rather than *A. perfoliata*. Diagnosis can be confirmed by microscopic examination of the parasite eggs, which are smaller than those of *A. perfoliata* and are oval. *A. mamillana* resides in the small intestine of the horse and is not killed by pyrantel. Praziquantel has high efficacy against this parasite. No evidence exists to suggest that the parasite is pathogenic, but the shedding of visible segments is often unacceptable to the owner. As with any other helminth infection, reinfection after treatment is likely. Owners should be warned that treatment with praziquantel every 6 to 12 months may be necessary.

## DISEASE PREVENTION

Ileal impaction colic, spasmodic colic, and possibly intussusceptions that are tapeworm-related are all potentially preventable. Worm control programs should include management of tapeworms to prevent the accumulation of large parasite burdens that are associated with an increased risk of colic. This can be achieved in two ways:

1. Targeted dosing. Using the tapeworm antibody ELISA, the tapeworm burden of all horses in the population can be assessed. Horses with test results indicating a high burden can be treated and a prophylactic dosing regimen commenced. Repeat testing of the whole population is suggested every 12 to 18 months.
2. Interval dosing. Horses on interval dosing regimens, or in circumstances where the tapeworm antibody ELISA is not readily available, can be given prophylactic doses of anthelmintic to prevent the development of high tapeworm burdens. Dosing every 6 months is suggested for high-risk horses (with a history of tapeworm-associated colic or other evidence of tapeworm infection), and yearly for lower risk horses (those with limited access to pasture or living in hot, dry climates).

The targeted approach has the advantage of periodically monitoring tapeworm status of the horses and allows control measures to be altered in response to changing patterns of infection. It also allows the identification of high-risk individuals and the concentration of treatment efforts on these animals.

A number of horse populations with an above-average incidence of colic have been identified as having a tapeworm problem. The investigation of any farm, livery yard or group of horses suffering an abnormally high incidence of colic should include evaluation of both strongyle and tapeworm status of all the horses (see Risk Factors Associated with Colic, *Current Therapy in Equine Medicine*, 4th ed.). Assuming adequate control because anthelmintics are regularly administered is insufficient. It is not uncommon to find tapeworm problems in groups of horses receiving frequent dosing with exclusively ivermectin preparations. In the absence of any antitapeworm prophylaxis, tapeworm burdens may have been allowed to reach high levels in certain animals. The nonrandom distribution of any parasite also makes the strategy of "random selection" of animals for testing a dangerous one. For a complete evaluation of parasite status, all horses in the population should be sampled. If tapeworms are identified as a risk factor for colic in a population, then treatment and prevention is relatively easy and inexpensive as outlined above.

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## CHAPTER 3.23

# Resistant Cyathostomiasis

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As cyathostomes have become recognized as the major pathogenic parasite of horses, resistance has developed to the anthelmintics used for their control. Once resistance to a particular anthelmintic is present, reversion to susceptibility is unlikely, and development of multiple drug resistance poses a serious risk to the health of the horse. Only three classes of anthelmintic are available for the horse: benzimidazoles (e.g., fenbendazole), tetrahydropyrimidines (e.g., pyrantel pamoate), and macrocyclic lactones (e.g., ivermectin, moxidectin). Therefore resistant cyathostomiasis must be managed in a way to preserve the efficacy of any remaining drugs and delay the development of further resistance, while providing continued protection against the pathogenic effects of cyathostomes. Control of resistant cyathostomiasis requires evaluation of the entire herd rather than an individual horse. Management of resistant cyathostomiasis requires knowledge of the behavior of the cyathostome and its interaction with the horse. In addition, the veterinarian must diagnose the extent of the problem, monitor for development of further resistance, and preserve efficacy of remaining drugs.

### CYATHOSTOME-HOST INTERACTION

The population dynamics of cyathostome infection in an individual animal and in the herd are complex, making control complicated. Eggs shed by mature females develop into infective L3 larvae on pasture. L3 consumed by the horse lose their protective sheath and migrate across the mucosa of the large colon and cecum, where they either become hypobiotic and encyst for periods of up to 2 years or develop into L4 larvae and excyst. Subsequently, larvae move across the mucosa back into the lumen, where they mature into adult cyathostomes.

Approximately 50 species of cyathostomes have been identified, and each has a different prepatent period (time from ingestion of infective larvae to production of eggs by the mature parasite) ranging from 5½ to 18 weeks. Only 8 to 10 species are common worldwide, but these have a similar wide range of prepatent periods. In young horses, the prepatent periods tend to be shorter, and greater proportions of infective larvae encyst and undergo arrested development than in adult horses.

At two points in the life cycle of a cyathostome it may not be exposed to anthelmintics: on pasture and in the mucosa of the cecum and large colon while encysted. Encysted larvae are under little selection pressure for development of resistance because many anthelmintics do not

gain access to these sites. However, as anthelmintics that have greater efficacy against encysted larvae become available, selection pressure for development of resistance may be increased. This is because larvae that subsequently mature already have been exposed to anthelmintic and survived treatment. Selection pressure for development of resistance in encysted populations may be reduced if larvicidal drugs are used sparingly in mature horses that would be expected to have low encysted populations and that have low fecal worm egg counts (FWEC), and which are therefore not contributing large proportions of the overall herd parasite load.

Knowledge of expected transmission patterns of free-living larval stages is essential in planning a control program, especially when trying to control resistant cyathostomiasis. In addition, FWEC are critical to devising a management plan. Survival and transmission patterns rely predominantly on environmental temperature, with daily minimum mean temperature probably the most important factor. In arid and dry tropical areas, rainfall is important for pasture infectivity, with greatest risk of infection during and immediately after the rainy season. Survival of eggs and larvae is generally good on pasture within the fecal pat in the presence of moisture and heat. However, if moisture and humidity are present year-round, periods of high rainfall may disrupt the effects of daily mean minimum temperatures by disseminating infective larvae over pasture, favoring larval survival. Optimum hatching of eggs and development to L3 occurs at 25° to 30° C, and rate of hatching is proportional to temperature. Development to L3 is retarded below 10° C, and below 4° C eggs remain viable but do not develop. Infective larval counts are greatest when daily minimum temperatures range between 4° to 18° C, and numbers of larvae on pasture are low when daily minimum temperatures are between 18° and 40° C and less than 0° C. The rate-limiting step at higher temperatures is the survival of L2, which increase their metabolic rate proportionally to temperature and thus may starve before they can develop to L3.

### DIAGNOSIS

Resistant cyathostomiasis is defined as a genetic condition in which an increasing frequency of the cyathostome population that was once killed by a drug survives treatment with that drug. In the early stages of resistance, the drug may remain clinically effective, but the proportion of resistant alleles increases in the cyathostome population. Eventually, the drug ceases to become clinically effective

but may still retain efficacy at higher doses. More potent drugs in the same class also may be efficacious initially, but as the proportion of resistant alleles in the population increases, these doses and more potent drugs also become ineffective. Indistinguishable from resistance is the problem of tolerance. Tolerance is defined as an innate lack of susceptibility to a drug by the parasite that did not arise from drug selection. Tolerance becomes clinically evident when the population of tolerant cyathostomes increases in a population to the extent that the anthelmintic used ceases to be effective in the cyathostome population as a whole. Currently, tolerance is included in the management recommendations for resistant cyathostomiasis because they are indistinguishable under field conditions.

The practicing veterinarian is most likely to become involved in investigating resistant cyathostomiasis as a clinical problem at one of two times: during routine evaluation of FWEC on a farm when treatment failure becomes evident, and during investigation of recurrent low-grade colic, weight loss, or poor performance. Treatment failure is defined as failure of anthelmintic treatment to reduce FWEC by at least 90% of pretreatment values within 10 to 14 days (fecal worm egg count reduction test). However, before diagnosing resistant cyathostomiasis, other causes of apparent treatment failure must be ruled out. These causes include underestimation of body weight (resulting in underdosing); failure of the horse to ingest all of the anthelmintic; rapid reinfection from heavily contaminated pastures; individual variability in pharmacokinetics of the drug; maturation of immature larval sources of cyathostomes not eliminated by the anthelmintic; and concurrent disease.

The McMaster technique for FWEC is the most commonly used by practitioners because centrifugation is not required. However, one of the limitations of this technique is technical error because parasite eggs rapidly become unequally distributed in the flotation solution. During sampling, the solution should be stirred constantly, and each side of the McMaster slide loaded rapidly and separately. Ideally, the count should be repeated in triplicate for each sample. A more sensitive and reliable technique is the modified Stoll's technique, but this test requires centrifugation. Because the daily egg output of an individual horse varies, the FWEC reduction test should be performed on an individual only when FWEC is more than 150 eggs per gram (epg). Changes in the FWEC reduction test may not be evident until 25% of the cyathostome population in a horse is resistant, and resistant alleles may be more prevalent than this. Resistance or tolerance therefore should be diagnosed when the FWEC reduction test is less than 95% so that delay in diagnosis is minimized as far as possible. Efficacy of pyrantel pamoate against cyathostomes has never been reliably more than 90%, so this level of reduction in egg output is acceptable for pyrantel pamoate but should be monitored closely. If dual resistant cyathostomes are present, such that the macrocyclic lactones are the only remaining susceptible drug group, then once a year, a modified FWEC reduction test should be considered in an attempt to identify development of resistance. Ideally, the horses under test should be housed for 21 days and their feces either composted or disposed of away from other horses. A FWEC reduction

test using 50% of the recommended dose of ivermectin should be performed, but the second FWEC should be taken at 7 days and the horse treated with the full-recommended dose at the same time. A second FWEC should be taken at 14 days, and if negative, then the horse can be released back onto pasture. The rationale for using 50% of the ivermectin dose is that when the full dose is used for the FWEC reduction test, early stages of drug resistance in more susceptible cyathostome species may be missed, because the marketed drug dose is calculated on the ability to kill the least susceptible species. If the FWEC reduction test is possible on only a few animals on a particular farm, then foals and horses younger than 2 years of age are likely to yield the most useful information.

Monitoring of egg reappearance time (ERT) after anthelmintic treatment is useful in assessment of drug efficacy. Egg reappearance time has been defined as the time until FWEC is more than 100 epg, greater than 10% to 20% of the pretreatment FWEC, or the time taken for any egg production to resume after anthelmintic treatment. When managing resistant cyathostomiasis, the veterinarian must be able to detect resumption of any egg production at an inappropriate time. Egg output should be suppressed for 6 weeks after fenbendazole treatment, 4 weeks after pyrantel pamoate, 8 weeks after ivermectin, and 12 weeks after moxidectin in the mature horse. These time intervals were once recommended for rapid interval dosing. Shortening ERT is one of the first indications that a cyathostome population may be developing resistance, or that the population structure is changing to favor those species capable of completing their life cycle within the treatment interval (a condition known as *anthelmintic avoidance*). Treatment of horses with an ERT less than the treatment interval should be considered carefully, because selection pressure for development of resistance is increased if the frequency of treatment is increased to control populations with a short ERT.

## ANTHELMINTICS

Resistance to the benzimidazoles is widespread. Cyathostomes resistant to pyrantel pamoate are becoming increasingly prevalent, and on some farms, resistance to both the benzimidazoles and tetrahydropyrimidines in the same population of cyathostomes has been demonstrated, leaving the macrocyclic lactones as the only effective drug group. Some populations of cyathostomes never previously exposed to anthelmintic have demonstrated tolerance to ivermectin.

Much attention has focused in recent years on the efficacy of anthelmintics against the mucosal encysted larvae, largely because of severity of clinical disease caused by the mass emergence of these encysted populations. Fenbendazole at 5 mg/kg and pyrantel salts have no efficacy against encysted stages. Ivermectin has limited efficacy against encysted stages. Moxidectin has moderate efficacy (62%-79%) against late L3 and L4 larvae. Only two drugs, moxidectin and fenbendazole (10 mg/kg PO q24h for 5 days; 7.5 mg/kg PO q24h for 5 days in Europe), are currently licensed for their larvicidal properties. Larvicidal doses of fenbendazole are not reliably efficacious against resistant adult cyathostomes, but resistance to the

benzimidazoles is already widespread, and therefore use of the benzimidazoles at larvicidal doses is unlikely to cause further resistance.

Concern exists that increasing the selection pressure for development of resistance by increasing exposure of developing larvae to macrocyclic lactones such as moxidectin, which have moderate efficacy against encysted stages leads to moxidectin resistance and hence ivermectin resistance. A further concern is the greater persistence of moxidectin in the host than ivermectin, so levels of moxidectin decline more slowly over time to sublethal drug levels. However, computer modeling suggests that the effect of greater potency of the drug offsets any potential selection by exposure to sublethal drug levels. Additionally, moxidectin retains some activity against incoming infective larvae for 2 to 3 weeks, and because ERT is at least 12 weeks, fewer treatments are required, which may reduce selection pressure. Larvicidal treatments should be used on horses newly arrived on a farm and when larval burdens would be expected to be high and pasture transmission low, so any larvae surviving treatment would be less likely to survive on pasture and be able to infect other horses.

The issue of underdosing is complex. Whether underdosing is dangerous in respect to the development of resistance depends on frequency of alleles for resistance already present in the population. If frequency of resistant alleles is low, underdosing allows more sensitive cyathostomes to survive, which may delay development of resistance. However, the converse is true if a high proportion of the population carries resistant alleles. The efficacy of daily pyrantel tartrate use in the face of pyrantel pamoate resistance has not been evaluated, and speculation exists regarding the contribution of daily pyrantel tartrate to the development of pyrantel pamoate resistance. If pyrantel tartrate is used as part of the cyathostome control program on an individual farm, then the efficacy should be monitored by regular FWEC on all treated horses.

Treatment frequency is recognized as the major contributing factor to the development of resistance. Therefore treatment frequency should be minimized. Several prevalent species of cyathostome are inherently tolerant to drugs commonly used for their control. For example, moxidectin has excellent efficacy against 19 species of cyathostome but is less efficacious against two species. Pyrantel pamoate has low efficacy against some species even at high doses. Therefore use at lower doses may select for populations not susceptible. Individual cyathostome species also possess a wide range of genetic diversity, and therefore some individuals in a species always will be more able to survive treatment than others. Administration of an anthelmintic drug selects for that individual or species that is able to survive treatment. The interaction between tolerance to one drug and resistance to another will likely become more problematic. Resistance to benzimidazoles has been confirmed in at least 13 species of cyathostomes, including the majority of the most common species encountered. Three of these species have demonstrated pyrantel salt resistance, and two of these species are only 90% to 99% susceptible to moxidectin. In computer modeling, examining development of resistance in sheep, efficacies of new drugs below 90% or above 99.9%

resulted in delayed development of resistance, whereas efficacies of 90% to 99.9% resulted in more rapid development of resistance. Therefore the risk of multiple drug resistance interacting with drug tolerance may result in species of cyathostomes not susceptible to any anthelmintic and therefore may comprise a larger proportion of the population than that which is susceptible.

## TREATMENT

No treatment exists for resistant cyathostomiasis. Reversion to susceptibility as judged by the FWEC reduction test may be seen after routine use of an anthelmintic ceases, but the proportion of resistant alleles in the population remains high, and evidence of resistance returns once the drug is again used. Resistant cyathostomiasis is managed by minimizing treatment frequency, selection of horses requiring treatment, selection of treatment, and careful management of grazing. This management must prevent clinical disease while allowing individual animals to acquire immunity to infection.

Drug selection requires that FWEC reduction testing and monitoring of ERT indicate acceptable efficacy in a given herd. At present, the macrocyclic lactones are the only drugs with reportedly reliable efficacy; however, use of other anthelmintics on farms should not be discounted until results of at least the FWEC reduction test are known. Many horse owners continue to use several classes of anthelmintic each grazing season to control tapeworms (*A. perfoliata*), bots (*Gastrophilus* spp.), and encysted small strongyles in addition to patent adult strongyle infection. This effectively constitutes a rapid rotation anthelmintic program, which has been shown by computer modeling to speed up development of drug resistance. If possible, the changeover time should be in the autumn, the optimal time for eradication of tapeworms and bots, so each horse receives one treatment with pyrantel and ivermectin annually. Additionally, owners should be educated to remove bot eggs from their horses' legs during grooming. If resistance is present to pyrantel pamoate, tapeworms should be managed by treating with pyrantel pamoate with an additional efficacious drug for cyathostomes given at the same time when FWEC dictates that treatment is necessary.

Once selection of the efficacious drug has been made, regular FWEC should be performed every 4 weeks on every horse on the farm. Mature horses should be treated with the efficacious drug when the FWEC reaches a level higher than 200 epg. Horses younger than 2 years of age should be treated when the FWEC reaches a level higher than 100 epg. The lower treatment threshold is used for young horses because they have poor immunity, so greater numbers of infective larvae encyst.

Monthly FWEC in the first year of the program are used to establish which horses are responsible for the majority of pasture contamination and to give some idea of the expected seasonal pattern of peak FWEC. In most parasite/host interactions, approximately 20% of hosts contribute 80% of the parasite load to the environment, and several studies have indicated that this is also true for horse transmission of cyathostomes. If these individuals are identified and treated as necessary, the risk of

transmission of heavy parasite loads to other horses, particularly to young horses, is reduced.

Certain types of farms carry heavier parasite loads. For example, FWEC are higher on stud farms, among horses used primarily for farm or ranch work and in horses younger than 3 years. However, no correlation exists between herd size and mean herd FWEC. In large herds of mature horses, in which FWEC on every animal is impractical, samples from at least 10 individuals or 10% of animals in the herd, whichever is greater, should be collected at the treatment interval of the drug being used and the whole herd treated when mean FWEC is greater than 200 epg. In groups of foals or young horses, treatment should be given for *Para-scaris equorum* at approximately 2 months of age. Then FWEC should be done every 4 weeks; the horses are treated again when FWEC are higher than 100 epg but not more frequently than the treatment interval of the drug. If *Para-scaris equorum* or *Strongyloides westeri* eggs are noted before strongyle eggs, then the foal should be treated appropriately. Once the initial 12-month monitoring period has established which mature horses have the highest FWEC, and which times of the year peak FWEC occurs, then FWEC can be reduced to 8 weekly intervals, or to monitoring at times of the year when peak FWEC are expected to occur.

Adequate worm control can be achieved even in the presence of resistant cyathostomiasis in young horses if grazing management is adopted. Collection of feces from the pasture twice weekly prevents hatching of larvae onto pasture and provides effective control. In herds of mature horses, this practice alone, in conjunction with monitoring of FWEC, likely obviates the need for treatment of cyathostome infection. However, all horses in this system should receive an appropriate anthelmintic once or twice yearly to control large strongyle and tapeworm infection.

Further means of reducing selection pressure for resistance and to preserve existing drugs include the following:

1. Treatment with anthelmintic only at times of the year when levels of free-living larvae on pasture are expected to be high. Use of climatologic data may be useful in planning the optimal time for anthelmintic treatments.
2. Temporary feed restriction for several hours before treatment, which may increase efficacy of drugs by slowing gut transit time.
3. Treating new arrivals and housing them for at least 72 hours should increase biosecurity. Ideally a FWEC should demonstrate no egg production before release on pasture.
4. Harrowing of pastures to expose larvae in the fecal pile to desiccation. This is an effective way of reducing the pasture load of infective larvae if humidity and rainfall is low, and temperatures are high. However, if these conditions are not met, harrowing tends to spread larvae to areas that have not been grazed.

### Supplemental Readings

- Dargatz DA, Traub-Dargatz JL, Sangster NC: Antimicrobial and anthelmintic resistance. *Vet Clin North Am Equine Pract* 2000; 16:515-536.
- Klei TR: Parasite control programs. In Robinson NE (ed): *Current Therapy in Equine Medicine*, 4th edition, pp 709-713, Philadelphia, WB Saunders, 1997.
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- Tarigo-Martinie JL, Wyatt AR, Kaplan RM: Prevalence and clinical implications of anthelmintic resistance in cyathostomes of horses. *J Am Vet Med Assoc* 2001; 218:1957-1960.

## CHAPTER 3.24

# *Lawsonia intracellularis* Proliferative Enteropathy

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**P**roliferative enteropathy (PE) is a transmissible enteric disease that affects a number of animal species, including the pig, hamster, fox, dog, ferret, rat, guinea pig, rabbit, monkey, ostrich, emu, sheep, deer, and horse. It has a worldwide distribution and its causal agent has been recently identified and classified as *Lawsonia intra-*

*cellularis*, an obligate intracellular bacterium. For pigs, in which the disease is best known, PE is transmitted by fecal-oral route and has an incubation period of 2 to 3 weeks. Proliferative enteropathy currently is not reported to be a zoonosis.

Although the usual source of contamination is not

transmission of heavy parasite loads to other horses, particularly to young horses, is reduced.

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Although the usual source of contamination is not

known, young animals intended for reproduction have been suggested as a possible reservoir for *Lawsonia* spp. in pigs. Recent findings indicate that the infection may last up to 10 weeks, during which pigs may shed the agent in their feces. Furthermore, *L. intracellularis* can survive up to 2 weeks in the environment. These findings suggest that the disease may be self-perpetuating in a herd of susceptible pigs after the introduction of an infected animal. It is uncertain whether PE infection is self-perpetuating in equine breeding farms. The incidence of PE in horses is unknown and although it has caused outbreak conditions in equine breeding farms, to date, most reports of the disease have involved single cases.

## CLINICAL PRESENTATION

Foals 4 to 7 months of age appear to be the most susceptible to the disease. In particular, weanlings seem to be predisposed to the infection. Clinical signs are variable but usually include depression, weight loss, subcutaneous edema, diarrhea, and colic. Extremely poor body condition with a rough haircoat and a pot-bellied appearance are common findings in severely affected foals. The progression and severity of the disease are variable. In some foals, death may occur after a short course of colic or diarrhea, whereas in others it may cause chronic growth retardation. Concomitant conditions such as upper or lower respiratory tract infection, intestinal parasitism, and dermatitis are also common findings.

## CLINICAL PATHOLOGY

Hypoproteinemia (<5.0 g/dl), primarily resulting from hypoalbuminemia, is the most consistent laboratory finding although not present in all cases. Other commonly observed abnormalities include leucocytosis, neutrophilia, anemia, increased creatinine kinase, hypocalcemia, hypochloremia, and hyponatremia.

## DIFFERENTIAL DIAGNOSIS

The clinical signs presented by foals with PE resemble those associated with common gastrointestinal diseases including acute intestinal obstruction, sand impaction, parasitism, gastroduodenal ulcers, and intoxication with plants and chemicals, including pharmacologic agents such as NSAIDs. Infectious agents that may be implicated in weanling diarrhea are numerous and include salmonellae, *Rhodococcus equi*, *Clostridium* spp., *Neorickettsia risticii*, *Campylobacter jejuni*, and rotavirus. However, these conditions are unlikely to cause outbreaks of disease characterized by weight loss, diarrhea, colic and severe hypoproteinemia in foals of this age group.

## DIAGNOSIS

Antemortem diagnosis of PE is based on the clinical signs, hypoproteinemia, and the exclusion of common enteric conditions. A thickening of segments of the small intestinal wall, as seen using abdominal ultrasonography, would further support the diagnosis. The presence of the *L. intracellularis* organisms can be detected using PCR analysis

of fecal samples. Although it is a specific technique, to date, PCR analysis has revealed a low sensitivity in horses. The use of serology for the diagnosis of *L. intracellularis* infection appears to be a promising tool to indicate previous exposure and possibly active infection.

Diagnosis of PE is confirmed based on the presence of characteristic intracellular bacteria within the apical cytoplasm of proliferating crypt epithelial cells of the intestinal mucosa using silver stains. Severe hyperplasia of the intestinal crypts often causes a grossly detectable thickening of the mucosa of the distal small intestine. PCR analysis and immunohistochemistry confirm the presence of *L. intracellularis* in intestinal tissue. Although the infection usually is confined to the jejunum and ileum, it may still be worthwhile to observe and biopsy the duodenal mucosa using endoscopy because a few cases reportedly have involved the anterior parts of the small intestine. Isolation of the organism is not a practical means of diagnosis as *L. intracellularis* cannot yet be cultivated in conventional cell-free media.

## THERAPY

Because *L. intracellularis* is an obligate intracellular bacterium, treatment of equine PE preferably should include an antimicrobial with good intracellular penetration. Erythromycin estolate (25 mg/kg PO q8-12h) alone or combined with rifampin (10 mg/kg PO q24h) for a minimum of 21 days is effective in controlling the disease. Chloramphenicol (50 mg/kg PO q6h) also appears to be efficacious. Other antimicrobials that also may be effective for the treatment of PE, based on MIC results using pig isolates, include chlortetracycline, penicillin, and ampicillin. In some foals additional symptomatic treatment such as antiulcer therapy and parenteral feeding may be required. Foals with severe hypoproteinemia benefit from the administration of plasma intravenously. Therapy should be aimed at controlling concurrent medical conditions when present. In clinical cases, the administration of symptomatic therapy alone is apparently ineffective at controlling the disease. However, in a foal with evidence of severe small intestinal obstruction, a surgical bypass of the affected area combined with the administration of an antimicrobial has lead to a favorable outcome.

## PROGNOSIS

Without appropriate antimicrobial therapy PE may lead to death. However, a rapid improvement (24-48 hours) in attitude, appetite, weight gain, and colic signs or diarrhea may be observed in foals after administration of erythromycin and/or rifampin. The plasma protein concentration does not respond quickly to therapy. The possibility of spontaneous recovery or subclinical infection, as reported in other species, has not been documented in the horse to date.

## PREVENTION

Factors that predispose weanling foals and pigs to PE are unknown. Young animals may be protected by colostral immunity and older animals may be immune because of previous exposure to the bacteria. In pigs, overcrowding, ration changes, antibiotic administration, mixing, and

transportation may be associated with the onset of the disease. These factors also are commonly encountered in foals after weaning and may contribute to equine PE.

### Supplemental Readings

Brees DJ, Sondhoff AH, Kluge JP et al: *Lawsonia intracellularis*-like organism infection in a miniature foal. J Am Vet Med Assoc 1999; 215:511-514.

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Schumacher J, Schumacher J, Rolsma M et al: Surgical and medical treatment of an Arabian filly with proliferative enteropathy caused by *Lawsonia intracellularis*. J Vet Int Med 2000; 14:630-632.

## CHAPTER 3.25

# *Clostridium difficile* Infection

K. GARY MAGDESIAN  
Davis, California

Until recently, the etiology of most cases of enterocolitis occurring secondary to antibiotic administration have remained unknown. However, with increasing diagnostic investigation, *Clostridium difficile* has been recognized as a significant pathogen associated with enterocolitis in horses and foals. *C. difficile* is a gram-positive, spore-forming obligate anaerobe linked to antibiotic-associated enterocolitis in a number of species. It is the most common cause of antibiotic-associated diarrhea, colitis, and pseudomembranous colitis in humans. Several other risk factors are associated with the acquisition of *C. difficile* disease in humans, including chemotherapy, ileus, and gastrointestinal manipulations, such as surgery, nasogastric intubation, repeated enemas, and endoscopy.

### CLINICAL MANIFESTATIONS

Four clinical manifestations of *Clostridium difficile* colonization occur in human patients:

1. Asymptomatic carrier state
2. Mild diarrhea without histologic evidence of colitis
3. Colitis
4. Pseudomembranous colitis

These syndromes apparently occur in horses as well. A number of host-agent interactions, including colonization resistance, host immunity, strain type, and virulence factors of the isolate, determine which syndrome predominates. Because of compromise to the normal gastrointestinal microbiologic flora during antimicrobial therapy, clostridia can overgrow and colonize the colonic mucosa. *C. difficile* spores are ingested from the environ-

ment or obtained by contact with asymptomatic shedders. Once ingested, spores can vegetate and proliferate within the enteral lumen. If the offending isolate is toxigenic, the elaboration of toxins leads to cytotoxicity and fluid accumulation within the gastrointestinal tract. The best studied of these toxins include toxin A (enterotoxin) and toxin B (cytotoxin), which act synergistically to cause enterocyte damage and loss of cell junction integrity. This causes subsequent inflammation, increased intestinal permeability, and the development of diarrhea. The gene sequence for binary toxin (ADP-ribosyltransferase) has been recently identified in equine *C. difficile* isolates. This toxin is believed to act as a cytotoxin in conjunction with toxin A and B.

Reports of *Clostridium difficile* infection in horses include outbreaks of diarrhea, individual cases of colitis, and large groups of horses with *C. difficile*-associated colitis. These descriptions have implicated several commonly utilized antibiotics in the pathogenesis of colitis, including  $\beta$ -lactam antibiotics, such as ampicillin, penicillin, and ceftiofur, as well as  $\beta$ -lactam antibiotics used in combination with gentamicin and sulfonamides. Other antibiotics reportedly associated with *C. difficile* infection include potentiated sulfonamides, sulfonamides and oral neomycin, dihydrostreptomycin, metronidazole, and erythromycin. The dams of foals being treated for *Rhodococcus equi* pneumonia with erythromycin and rifampin are reportedly susceptible to colitis with *C. difficile*. Although all of the risk factors for establishment of *C. difficile* disease in horses have not been determined, antibiotic administration appears to be an important contributor. The roles of gastrointestinal surgery, the administration of other thera-

transportation may be associated with the onset of the disease. These factors also are commonly encountered in foals after weaning and may contribute to equine PE.

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peutics such as nonsteroidal antiinflammatory drugs, dietary components, transportation, colic, and ileus in the pathogenesis of equine *C. difficile* colitis are unknown. In the author's experience, anorexia and other stressors, such as shipping, may contribute to the development of colitis, particularly when present in conjunction with antimicrobial administration. The mortality rate has been reported to be higher in horses with *C. difficile*-associated colitis than in *C. difficile*-negative cases.

## CLINICAL SIGNS

The clinical presentation of horses with *C. difficile*-associated colitis varies from asymptomatic colonization through mild diarrhea to severe colitis. The clinical signs are the result of an inflammatory response to endotoxemia and are similar to those observed with colitis of other etiologies. Pyrexia or subnormal body temperatures, tachycardia, and tachypnea are consistent with a systemic inflammatory response syndrome (SIRS). Other clinical signs include lethargy, ileus to hypermotility, congested and injected mucous membranes, dehydration, and hypovolemia. Severely affected individuals may present with adynamic ileus and a paradoxical lack of fecal production despite severe colitis. Such horses demonstrate signs of severe abdominal pain and may be difficult to differentiate from those with strangulating or obstructive gastrointestinal lesions. Horses with *C. difficile* colitis are at risk for developing secondary complications including edema, laminitis, thrombophlebitis, coagulopathies, bacteremia, and intestinal perforation. Obtundation, loss of suckle, and abdominal distention, with or without signs of colic, are common in neonatal foals with *C. difficile* enterocolitis.

## CLOSTRIDIUM DIFFICILE INFECTION IN NEONATAL FOALS

*C. difficile* can infect neonates as a primary pathogen; antibiotic use is not a prerequisite for development of infection. Two syndromes have been described in foals: self-limiting, watery diarrhea, and severe, highly fatal hemorrhagic enteritis. Both individual cases and outbreaks of diarrhea have been described. *C. difficile* should therefore be a part of the differential diagnostic list for any neonatal foal presented for diarrhea.

In this author's experience, a subclinical carrier state is common in hospitalized neonatal foals. The role of antibiotic administration in colonization of these patients is unknown. It is unclear why these neonates do not develop diarrhea or other clinical signs of *C. difficile* infection. A high prevalence of symptomless colonization has been well documented in human neonates that are group-housed. More than 50% of asymptomatic infants are colonized transiently with toxigenic *C. difficile* isolates in some nurseries and hospitals. Current hypotheses for the lack of clinical disease in these patients include protection from the effects of *C. difficile* toxins by binding of toxin A to IgA or secretory components of milk. Others include the theory that infant enterocytes lack receptors or receptor sensitivity for *C. difficile* toxins. It is unknown whether these factors also play a role in protecting equine neonates from disease.

## DIAGNOSIS

Definitive confirmation of *C. difficile* as the cause of enterocolitis can be difficult. The diagnosis is contingent on history, exclusion of other etiologic agents, and the identification of the organism and its toxins in fecal samples. *C. difficile* should be suspected in any horse that develops diarrhea subsequent to antimicrobial administration. In perinatal foals, however, *C. difficile* may act as a primary pathogen. Other potential pathogens, including salmonellae, *Neorickettsia risticii*, and encysted cyathostome larvae, should be ruled out based on history and ancillary diagnostic testing. *Aeromonas* spp. and *Clostridium perfringens* may play a role in antibiotic-associated colitis; however, their exact role in such diseases is unclear. *Lawsonia intracellularis* and *Rhodococcus equi* should also be considered in suckling and weaning foals, and agents to be considered in the differential diagnosis of neonatal enterocolitis include *C. perfringens*, salmonellae, rotavirus, coronavirus, cryptosporidia, and *Strongyloides westeri*.

Samples for diagnosis of *C. difficile*-associated colitis should be tested as soon as possible after collection. Testing should include fecal culture and toxin assays. For shipping to outside laboratories, fecal specimens should be refrigerated and stored in airtight containers; alternatively, fecal swabs can be inoculated into anaerobic transport media for culture purposes. For toxin assays, feces should be refrigerated or frozen if testing is to be delayed. Several grams of feces should be collected because swabs are inadequate for toxin testing.

Culture of the organism is enhanced by growth on specific plates or in broth containing cycloserine, cefoxitin, and fructose agar (CCFA). A presumptive identification of *C. difficile* can be made from colonial morphology on selective media, in conjunction with gram-staining characteristics. *C. difficile* colonies are flat, irregular, yellow-white to grayish in color, and have a "ground glass" appearance. They are gram-positive rods and may demonstrate oval subterminal spores. Microbiology laboratories confirm isolates growing on CCFA as *C. difficile* through cell wall fatty acid analysis or through evaluation for the presence of a specific antigen of *C. difficile* (glutamate dehydrogenase or L-proline-aminopeptidase). Some isolates of *C. difficile* are nontoxigenic, and others may produce only one toxin. The role of nontoxigenic isolates is unclear and not thought to affect most patients. Strains producing only one toxin, either toxin A or B, however, are currently considered potentially pathogenic in human patients.

A fecal cytotoxin assay using cell tissue culture is available but is time consuming and costly and tests only for the presence of toxin B. A number of commercial fecal ELISA kits, developed for human medicine, have been used in horses. ELISA toxin testing is readily available, inexpensive, and rapid. Some of these test for the presence of toxin A, whereas others test for both toxins A and B. These bivalent assays are most useful because they detect toxin production from isolates producing only one toxin. Some ELISA tests also detect the presence of *C. difficile* antigens in feces. PCR techniques are available for detection of toxin A and B gene sequences in cultured isolates.

Occasionally, culture positive cases are negative for the presence of toxin A in fecal samples tested with ELISA kits.

Possible causes for this discrepancy include the following:

1. Infection with isolates producing only toxin B
2. Colonization with nontoxigenic strains
3. Lack of sensitivity of the toxin assay used
4. Degradation of toxins resulting from sample-handling errors
5. Intermittent or low level toxin production

Thus more than one fecal ELISA may be required to detect toxin. If still negative on repeated assays, the cultured isolates should undergo PCR testing for the presence of toxin genes. If positive, the author considers such cases as highly suspect and treats them as *C. difficile* cases after ruling out other potential etiologies. Whether such isolates produce toxins *in vivo* is unknown.

Gram staining of feces can be an early indicator of clostridial involvement while other diagnostic test results are pending. Although not specific for *C. difficile*, a predominance of gram-positive rods can provide the clinician with a suggestion that clostridial microorganisms may be involved.

In addition to these specific diagnostics, horses with *C. difficile* colitis should have complete clinical pathologic evaluations that aid in directing therapy. Complete blood counts, serum biochemistry profiles, arterial and/or venous blood gases, and coagulation panels should be evaluated whenever possible. A toxic, left shift and neutropenia are common findings in horses with *C. difficile*-associated colitis. An increase in hematocrit and hypoalbuminemia are frequent findings. Blood lactate and plasma colloid oncotic pressures may provide additional information regarding response to treatment and prognosis. Passive transfer of maternal antibodies is often adequate in foals developing clostridial enterocolitis. Analysis of peritoneal fluid in cases of *C. difficile* colitis reveals a transudate to exudate.

Diagnostic imaging is useful in horses exhibiting signs of abdominal pain. Transabdominal ultrasonography may reveal thickened and hypomotile large bowel in adult animals. Thickened, nonmotile and fluid-filled loops of small intestine may be present in neonates. Abdominal radiography is most informative in neonates, which may show gas and fluid-filled small and large intestinal loops.

## TREATMENT

Treatment of *C. difficile* disease depends on clinical severity. Discontinuation of the offending antimicrobial may be all that is required in horses with mild diarrhea and without signs of a systemic inflammatory response syndrome. Halting the use of systemic antibiotics that are associated with the onset of colitis is a vital step in treating horses with *C. difficile*. In most cases, the colitis itself is more life threatening to the equine patient than is the primary disease. When systemic antibiotics are vital, however, alternative antibiotics with less potential to disrupt the intestinal flora should be selected. Horses with more severe diarrhea and colitis may require intravenous fluid therapy and supportive care, in addition to specific antibiotics directed against the clostridial agent. Metronidazole, bacitracin, and vancomycin are the antibiotics used to treat humans with *C. difficile* infections. Metronidazole is the first-line antibiotic used in most

cases. It is preferred over vancomycin because of lower cost and less selection pressure for vancomycin resistance. Vancomycin is used judiciously because it is reserved for multi-drug-resistant enterococci and staphylococci. Bacitracin is more costly and less effective than metronidazole and is therefore not considered a first-line agent in the treatment of *C. difficile* diarrhea in people.

Metronidazole (15 mg/kg q8h PO; neonates: 10 mg/kg q8-12h PO) should be considered a front-line therapeutic in horses with *C. difficile*-associated colitis. However, equine isolates of *C. difficile* in one specific region of California have been shown to be resistant to metronidazole. In these horses, metronidazole therapy often preceded the development of diarrhea. Fortunately, studies evaluating the susceptibility of *C. difficile* isolates from other areas have failed to demonstrate resistance. Horses treated with metronidazole should be monitored for side effects, including anorexia, depression, neurologic deficits, and hepatotoxicity. These signs can be mistaken as manifestations of colitis and warrant careful monitoring of the patient. Treatment should continue for 7 to 10 days or until the diarrhea resolves. Bacitracin appears to be uniformly ineffective against equine *C. difficile* isolates, as demonstrated by *in vitro* susceptibility testing of a large number of isolates. Based on these findings, bacitracin is not recommended for treating horses with *C. difficile*. Although effective, vancomycin use should be restricted to minimize selection pressure and the development of resistance in other bacteria. Its use should be limited to those cases not responding to metronidazole and supportive therapy, and when susceptibility testing of isolates demonstrates metronidazole resistance.

Supportive therapy should be directed at correcting fluid, electrolyte, and acid-base balance. Colloids, in the form of hetastarch or plasma, may be indicated to treat hypoalbuminemia. Combating the effects of endotoxemia and SIRS, as with other causes of colitis, is part of the therapy of *C. difficile* infections. Nutritional support should be provided to horses and foals that are anorexic. Systemic antibiotics should be avoided whenever possible. This author utilizes aminoglycosides in horses that are febrile or markedly neutropenic, to prevent bacterial translocation and bacteremia with gram-negative enteric organisms. Aminoglycosides, such as gentamicin or amikacin, lack activity against anaerobic bacteria and distribute poorly into the gastrointestinal lumen, thereby having relatively little effect on the normal flora. Because of risks for septicemia secondary to bacterial translocation, neonates with enteritis should be treated with broad-spectrum antibiotics. Lactose intolerance has been reported secondary to *C. difficile* enteritis in neonatal foals. Lactase supplementation (6000 FCC U PO q3-4h) may be beneficial in affected suckling foals.

Various additional therapeutic approaches have been utilized in management of *C. difficile* infections in humans. These include cholestyramine, bacteriotherapy with fecal enemas, oral administration of nontoxigenic *C. difficile*, and treatment with the yeast *Saccharomyces boulardii*. These agents have not been evaluated in horses, and the use of probiotics in horses with colitis has not been investigated thoroughly.

## PREVENTION

Prevention of *C. difficile* rests with judicious and careful antimicrobial use. Horses being treated with systemic antibiotics should be monitored closely for a reduction in appetite, in addition to changes in fecal character. Partial anorexia and slight softening of the feces warrant a temporary discontinuation of the antimicrobials. Additional stressors, such as transportation, should be minimized in horses treated with antibiotics. The dams of foals being treated with macrolides for *R. equi* infections also should be monitored closely for anorexia and diarrhea. Feed and watering bins should be cleaned regularly, and feces from these foals should be removed frequently. This minimizes exposure of mares to low levels of macrolide antibiotics and clostridial organisms.

Isolation of infected horses is important to minimize environmental contamination with spores because they are highly resistant to disinfection and environmental extremes. In addition, isolation minimizes the exposure of young foals or horses on antimicrobials to large numbers of *C. difficile*.

## Supplemental Readings

- Baverud V, Franklin A, Gunnarsson A et al: *Clostridium difficile* associated with acute colitis in mares when their foals are treated with erythromycin and rifampin for *Rhodococcus equi* pneumonia. *Equine Vet J* 1998; 30:482-488.
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- Jones RL: Diagnostic procedures for isolation and characterization of *Clostridium difficile* associated with enterocolitis in foals. *J Vet Diagn Invest* 1989; 1:84-86.
- Magdesian KG, Madigan JE, Hirsh DC et al: *Clostridium difficile* and horses: a review. *Rev Med Microbiol* 1997; 8(Suppl 1):S46-S48.
- Weese JS, Staempfli HR, Prescott JF: A prospective study of the roles of *Clostridium difficile* and enterotoxigenic *Clostridium perfringens* in equine diarrhoea. *Equine Vet J* 2001; 33:403-409.

# CHAPTER 3.26

## Liver Disease

SIMON F. PEEK  
Madison, Wisconsin

**L**iver disease occurs commonly in adult horses and less commonly in foals. Clinicians usually are alerted to liver dysfunction by serum biochemical investigation of a sick individual with clinical signs that suggest hepatic or hepatobiliary disease. Rarely can a presumptive diagnosis of liver disease be made purely on the basis of a physical examination, usually when signs of fulminant hepatic failure are present, including encephalopathy and severe jaundice. When liver disease is suspected clinically, further diagnostic testing is warranted to investigate the severity of the biochemical abnormalities, to formulate the most appropriate therapeutic plan, and to provide a prognosis. Although both acute and chronic liver failure carry a poor to grave prognosis, whatever the cause, the immense reserve capacity of the liver provides substantial opportunities for successful therapeutic intervention when an early diagnosis is made and an aggressive approach taken in an animal with less severe liver disease.

## DIAGNOSIS

### Biochemical Tests

Standard biochemical indices of hepatocellular disease include sorbitol dehydrogenase (SDH), aspartate aminotransferase (AST), isoenzyme 5 of lactate dehydrogenase

(LDH-5), and ornithine carbamoyltransferase. Although SDH is the most specific indicator of acute hepatocellular damage, all diagnostic laboratories do not perform quantification of SDH and caution is warranted with sample handling and processing. The enzyme is stable at room temperature for a maximum of 12 hours. If any delay in processing is anticipated, the serum or plasma must be separated and preferably frozen before quantification. SDH possesses a short half-life of just a few hours in blood so that levels quickly return to normal.

The other commonly measured hepatocellular enzyme is AST. However, it is poorly specific and is released commonly with myopathic conditions. It has a much longer half-life, and consequently elevated blood levels may persist for well beyond a week after resolution of the inciting event. LDH-5 also suffers from poor specificity, being released from muscle tissue, but has a half-life of less than 24 hours.

Commonly examined enzymatic serum biochemical indices of hepatobiliary disease are  $\gamma$ -glutamyl transferase (GGT) and alkaline phosphatase (AP). GGT is the more specific indicator of biliary epithelial damage, being released into serum as a result of a variety of inflammatory and obstructive hepatobiliary, in addition to cholestatic diseases. AP can be released from a number of sites, including bone (especially in young foals), intestine, and

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placenta. The half-life of GGT in horse blood is unknown but by analogy with other mammalian species in which it varies between 2 and 4 weeks, most likely equine GGT has a half-life at least as long as that of AST.

Elevations in AST, SDH, GGT, and AP occur with most of the common hepatocellular and hepatobiliary diseases, and they are not diagnostically mutually exclusive. The proportionate increases in GGT and AP versus AST and SDH can be helpful in suggesting a diagnosis of either hepatobiliary or hepatocellular disease. Cholangiohepatitis, for example, causes proportionately much greater increases in GGT and AP compared with SDH and AST, whereas the reverse is true of hepatocellular conditions such as Tyzzer's disease in adults or Tyzzer's disease in foals.

Serum bile acids consistently are elevated with both hepatocellular and hepatobiliary diseases and are not indicative of a particular etiology, although they do tend to be proportionately more elevated with hepatobiliary diseases. Although obtaining fasting samples for accuracy is unnecessary, unlike in other species, moderate increases in total serum bile acids up to 20  $\mu\text{mol/L}$  may be seen with prolonged anorexia in adults regardless of the primary disease.

Serum or plasma bilirubin levels are elevated in horses with both hepatocellular and hepatobiliary diseases but mild hyperbilirubinemia also can develop rapidly in horses that are anorectic, regardless of the reason. Both unconjugated (indirect reacting) and conjugated (direct reacting) bilirubin can be valuable diagnostically. Elevations in the conjugated fraction, to greater than 25% of the total bilirubin value, indicate cholestatic/hepatobiliary disease. Clinically evident jaundice with marked unconjugated hyperbilirubinemia always should suggest hemolytic disease if no other biochemical evidence exists of hepatocellular or hepatobiliary disease.

Accurate blood ammonia measurement requires rapid and careful sample handling. Ideally, a control sample should be obtained from a healthy horse and quantitated simultaneously for comparative purposes. Values in excess of 100  $\mu\text{mol/L}$  should be considered abnormal.

Dye excretion tests such as the bromosulphophthalein test, and the less commonly discussed indocyanine green, aminopyrine, and caffeine clearance tests have become anachronisms. In some cases, the reagents are no longer even readily available.

In foals, many standard indices of liver function/disease possess considerably different reference ranges than in adults. GGT, bile acids, and alkaline phosphatase, for example, are elevated in healthy foals compared with adults, and readers are directed to refer to Kotterba's *Equine Clinical Neonatology* (see readings list) for age-specific normal ranges in foals.

### Liver Ultrasound

Transabdominal ultrasound and ultrasound guided liver biopsy should be part of the diagnostic approach to undifferentiated hepatic disease. Ultrasonographic examination of the adult equine liver is best performed with either a 2.5-MHz or 5-MHz transducer. In neonatal foals a 7.5- or 10-MHz scanner is capable of effectively imaging the

entire liver, but in older and weanling age foals, a 5-MHz probe is required. In both adults and foals, the liver is best imaged from the right, immediately caudal and ventral to the right lung. Typical anatomic landmarks for liver imaging are the sixth to fifteenth intercostal spaces on the right and the sixth to the ninth intercostal spaces on the left. In neonatal foals the liver also can be imaged from a ventral position just caudal to the xiphoid.

In adults, the ease of liver imaging is variable, depending upon the nature of the underlying condition (hepatomegaly versus fibrosis), normal age changes (right lobe atrophy in middle-age to older horses), and other factors such as the extent of the lung fields, gas distention of the colon, and presence and severity of splenomegaly. Healthy liver tissue is less echogenic than the spleen and has a much more prominent vascular pattern. The portal veins can be distinguished from the hepatic veins by the greater amount of fibrous tissue lining the walls of the portal vasculature. Bile ducts are not normally visible and their presence indicates impaired biliary outflow, the most common reason for which is suppurative cholangiohepatitis/choledocholithiasis.

### Liver Biopsy

When clinical and serum biochemical evaluation of an individual provides evidence of hepatic disease, a definitive diagnosis often requires liver biopsy. Although a presumptive diagnosis often can be reasonably made based on history, clinical signs, and bloodwork a definitive diagnosis of the extent and severity of disease can be obtained only after biopsy.

Ultrasound greatly facilitates the biopsy procedure. Veterinarians may be frustrated when attempting to obtain liver biopsy material without ultrasonographic guidance and using only the standard anatomic landmarks of the intersection between a line drawn from the point of the shoulder to tuber coxae and the fourteenth intercostal space. Without ultrasonographic guidance, liver tissue may not be obtained, and the veterinarian runs the risk of inadvertently obtaining a biopsy from the colon, diaphragm, or lung. The size, location, and accessibility of the liver to percutaneous biopsy varies with the type and progression of the underlying condition. Acute cholangiohepatitis can cause significant hepatomegaly so that the liver may be readily accessible on both right and left sides of the abdomen. Progressive fibrosis and parenchymal loss in that same horse eventually may cause such a small liver that it can be challenging to find a transabdominal "window" through which a biopsy can be performed safely.

Sufficient liver material should be obtained for at least conventional light microscopy. The pathologist should report both the predominant cellular population(s) in any inflammatory infiltrate and the presence and extent of any periportal or bridging fibrosis. Biliary hyperplasia occurs with almost every hepatic and hepatobiliary disease and its significance should not be overinterpreted. Prognosis requires stains that show the presence and severity of fibrosis, particularly with conditions such as cholangiohepatitis, chronic active hepatitis, and pyrrolizidine alkaloid toxicity that tend to be associated with chronic, insidious, or recurrent hepatic injury and progressive parenchymal fibrous tis-

sue replacement. Generally speaking, the presence of mature collagen (as identified via Masson's Trichrome stain) that fully bridges between portal tracts is a poor prognostic sign, whereas minimal or absent fibrosis confers a much more favorable prognosis in cases of inflammatory hepatitis/cholangiohepatitis or pyrrolizidine alkaloid toxicosis. However, some horses have survived more than 2 years after identification of bridging periportal fibrosis in conjunction with a primary hepatic lesion of either suppurative cholangiohepatitis or chronic active hepatitis.

Prebiopsy evaluation of extrinsic, intrinsic, and common clotting function, by measurement of prothrombin time (PT) and activated partial thromboplastin time (APTT) often is recommended. A control sample from a normal horse also should be submitted for quality control purposes. After biopsy, ultrasonography can be helpful to identify significant hepatic hemorrhage from biopsy sites. Although prolonged clotting times are rare even with fairly severe liver disease, Theiler's disease, Tyzzer's disease, and end-stage pyrrolizidine alkaloid toxicity are notable exceptions to this. Therefore this author does not recommend liver biopsy for adults that present with signs suggestive of Theiler's disease, or in foals with clinical and biochemical evidence of liver failure.

To obtain sufficient biopsy material for histologic evaluation, a 14-gauge Tru-cut biopsy device (Mila Medical, Chicago) is recommended. Smaller devices provide insufficient material. When history, presenting signs, and biochemical evaluation suggest a diagnosis of cholangiohepatitis, liver tissue also should be submitted for both aerobic and anaerobic culture. For optimal chance of a positive culture, all antibiotics should be withdrawn for at least 48 hours before the procedure and the liver tissue should be placed directly into appropriate growth media at the time of sampling. Several 14-gauge liver biopsy samples can be obtained safely in an adult horse, provided no corroborating biochemical evidence exists of biosynthetic liver failure and protracted clotting times.

## DIFFERENTIAL DIAGNOSIS

The following is a summary of the important hepatic conditions documented in adults and foals. More comprehensive coverage can be found in *Current Therapy in Equine Medicine*, fourth edition, p. 253.

The list of commonly encountered liver diseases in foals is quite short (Box 3.26-1) and some of the toxic hepatopathies (such as iron fumarate toxicity) are rare. However a number of conditions are more common causes of elevated liver enzymes in neonatal, nursing, and weanling age foals. Significant elevations in hepatocellular and hepatobiliary enzymes occur in cases of neonatal sepsis, but severe fulminant liver failure with massive elevations in SDH, GGT, hyperbilirubinemia, hypoalbuminemia, hypoglycemia, and concurrent neurologic signs should raise a suspicion of Tyzzer's disease. Occasionally septic neonatal foals develop fulminant acute liver failure. Moderate elevations in serum GGT frequently are seen in foals with clinically significant gastroduodenal ulceration especially with pyloric outflow obstruction and stricture formation. Whether this represents restricted bile outflow through the sphincter of Oddi or bile stasis and incomplete intrahe-

### BOX 3.26-1

#### Differential Diagnoses for Liver Disease in Adult Horses and Foals

##### Hepatic Conditions of Adult Horses

Theiler's disease  
Cholangiohepatitis/choledocholithiasis  
Chronic active inflammatory hepatitis  
Pyrrolizidine alkaloid toxicosis  
Hyperlipemia of ponies/miniature horses  
Hepatic abscessation  
Toxic hepatopathies  
Hepatic/biliary neoplasia

##### Hepatic Conditions of Foals

Tyzzer's disease  
Toxic hepatopathies  
Hepatitis due to bacterial sepsis  
Equine herpesvirus (EHV)-1 hepatopathy

patic biliary clearance resulting from abnormal peristalsis is uncertain. A similar elevation in serum GGT, unaccompanied by other biochemical evidence of liver disease occurs in mature horses with protracted anterior enteritis, or postoperative small intestinal ileus causing persistent proximal reflux. Foals with *Rhodococcus equi* pneumonia that have elevations in hepatobiliary enzymes, particularly GGT, should be evaluated for possible intraabdominal abscesses. Umbilical vein remnant infection with or without concurrent liver abscessation is an unusual but occasional cause of mild liver enzyme elevation.

In addition to the primary hepatic conditions in adults (see Box 3.26-1), right-sided heart disease can be associated with liver enzyme elevations, especially GGT and AP. Although no prognostic value can be attached to the absolute value of these enzymes, the presence of significant elevations in GGT, particularly if ascites also is visible ultrasonographically, is consistent with congestive heart failure. Occasional isolated elevations in GGT may be seen in mature horses with surgical conditions of the large colon, particularly large colon torsions or long-standing displacements, possibly because of tension on the duodenocolic ligament.

Significant elevations in hepatocellular and hepatobiliary enzymes can be seen in association with hepatic lipid infiltration secondary to hyperlipemia in miniature horses, ponies, and donkeys, although it may occasionally occur in adult horses with concurrent severe catabolic disease. Although aggressive therapy for the hyperlipemia (enteral or parenteral nutritional support, polyionic fluids) may be associated with clinical and biochemical improvement, concurrent azotemia suggestive of renal parenchymal lipid infiltration in addition to biochemical evidence of hepatic lipidosis should warrant a guarded prognosis.

Where pyrrolizidine alkaloid toxicity is known to occur, the identification of an individual with clinical signs of significant chronic liver disease (weight loss, jaundice, photosensitization) verified by liver enzyme elevations

and/or biopsy should encourage biochemical screening of other horses on the premises. Clinically healthy horses may be identified in at-risk populations that demonstrate abnormal enzymology; for these horses therapeutic intervention and dietary management may make a significant long-term impact.

## THERAPY

The therapy of liver disease is frequently nonspecific, but the results of further diagnostic testing, particularly ultrasound guided liver biopsy, culture, and histopathology can be particularly useful in selection of a more specific therapeutic plan and provision of greater prognostic information to the client. The results of liver biopsy evaluation can be of particular relevance in selecting specific therapies such as corticosteroids/colchicine for chronic inflammatory hepatopathies with fibrosis, or the selection of a specific antibiotic based upon culture and sensitivity testing of biopsy material from a horse with suppurative cholangiohepatitis. Dietary management also can be an important facet of the therapy for several forms of acute and chronic hepatic disease.

### Hepatic Failure

Treatment of hyperammonemic hepatic encephalopathy should reduce further ammonia production and absorption and provide nonspecific supportive measures for the fulminant hepatic failure that typically accompanies hepatic encephalopathy. The acidifying agent lactulose (90-120 ml PO, q6h) decreases ammonia absorption from the large intestine by converting ammonia to ammonium ions, which are not absorbed from the lumen. In addition, oral antibiotics such as neomycin (20-30 mg/kg q6h), or metronidazole (10-15 mg/kg q6h) may be administered to decrease ammonia-producing bacteria within the large intestine. Drugs may be administered orally by dose syringe in molasses or Karo syrup to avoid epistaxis when nasogastric intubation is attempted because digested blood adds to the ammonia load of an already failing liver.

A priority in the therapy of affected horses is sedation and relief from the anxiety and occasionally dangerous mania that they demonstrate, for the patient and those around them. Nonspecific measures for the treatment of fulminant hepatic failure should include intravenous fluids to maintain tissue perfusion and to correct specific electrolyte and acid-base abnormalities.

Hypoglycemia often accompanies fulminant hepatic failure in foals and adult horses with Theiler's disease, and when present should be treated by infusion of 5% or 10% dextrose. Supplemental potassium should be added to the fluid protocol, particularly when dextrose is being infused, because the latter causes intracellular shifting of potassium in what is often already a hypokalemic individual.

If hypoalbuminemia (serum albumin <2.0 g/dl) is documented, fresh blood, plasma, or plasma expanders should be considered. Fresh blood is a valuable, although transient, source of clotting factors if the affected individual has protracted clotting times. The addition of bicarbonate to intravenous fluids should be considered when systemic pH falls below 7.1. Because cytotoxic cerebral

edema frequently complicates hyperammonemic hepatic encephalopathy, horses with this condition must not be overhydrated and plasma oncotic pressure must be maintained. Administration of dimethylsulfoxide or mannitol also may be considered to diminish cerebral edema in horses that suffer from hepatic encephalopathy.

### Cholangiohepatitis and Choledocholithiasis

Because the etiopathogenesis of cholangiohepatitis and cholelithiasis in adult horses is suspected to involve ascending bacterial infection from the proximal small intestine, long-term antimicrobial therapy is critical in the treatment of this condition. If biliary obstruction is complete and/or the horse experiences intractable abdominal pain, surgery may be considered.

The choice of specific antibiotics ideally is based on aerobic and anaerobic cultures of liver biopsy material. However, if culture results are either unavailable or negative, then broad-spectrum antibiotics such as potentiated sulfonamides, cephalosporins, or fluoroquinolones are appropriate choices. Although the spectrum of activity of the aminoglycosides is limited to aerobic, gram-negative bacteria, a good clinical response to this family of antibiotics often is observed. Antibiotic treatment should be continued until serum GGT and AP levels have been normal for 2 to 4 weeks. In many cases, this requires a protracted period of therapy. Treatment failure can be associated with premature antibiotic withdrawal, so it is worth continuing treatment until both clinical and biochemical resolution has been confirmed. Many horses show substantial clinical improvement in terms of appetite, absence of fever, and weight gain while still demonstrating continuing and significant biochemical evidence of hepatobiliary disease.

Repeated ultrasonographic evaluation of the liver during the course of therapy can be useful in assessing improvements in hepatomegaly and bile duct dilatation and the resolution of identifiable calculi. Intravenous polyionic fluid therapy can be a useful adjunct to antimicrobial therapy in cases of acute cholangiohepatitis and during long-term therapy, when an individual horse clinically deteriorates. DMSO may have some benefit in the dissolution of calcium bilirubinate calculi, which represents the majority of equine choledocholiths and hepatoliths.

### Chronic Nonsuppurative Inflammatory Hepatitis

The etiopathogeneses of the nonsuppurative chronic active hepatopathies in horses are poorly understood but lymphocytic; eosinophilic and plasmacytic infiltrates have all been described. The therapeutic usefulness of corticosteroids has not been evaluated thoroughly but makes empiric sense for several forms of chronic liver disease. Corticosteroid administration should be restricted to horses with histologically confirmed nonsuppurative hepatitis/cholangiohepatitis. Probably the most common histologically confirmed form of equine liver disease for which corticosteroids are indicated is chronic active hepatitis, although many cases of histologically confirmed nonsuppurative cholangiohepatitis/hepatitis apparently



benefit from corticosteroid treatment. Dexamethasone at a dose of 0.05 to 0.1 mg/kg for 5 to 7 days followed by a gradual reduction in dose over a 2- to 4-week period can be used for treatment of histologically confirmed non-suppurative inflammatory hepatitis. Alternatively, horses may be placed on prednisolone (up to 1 mg/kg daily) for an extended period of several weeks, although when withdrawing therapy the prednisolone dosage should be reduced gradually over an additional 2- to 4-week period. Corticosteroids also may have a role in the therapy of horses with fibrosis as a means of reducing further collagen production and maturation.

Colchicine is an antifibrotic agent that inhibits collagen production, enhances hepatic collagenase activity, and interferes with collagen maturation, and as such it would appear to be therapeutically attractive in horses with histologically confirmed fibrosis. However, no controlled studies evaluate its efficacy or safety in horses, and the drug has proven limited in a variety of different human hepatic disorders. Colchicine should be given for an extended period of several weeks to months to mediate any beneficial effect on long-term survival. The drug can be used in horses at a dose of 0.01 to 0.03 mg/kg orally for several weeks without adverse side effects.

### Pyrrolizidine Alkaloid Toxicosis

The most important aspect of therapy for the horse with pyrrolizidine alkaloid toxicosis is removal of the animal from exposure to the offending plants in hay or pasture. Unfortunately, by the time many animals are clinically affected, such severe parenchymal loss and fibrotic change occur that any treatment offered is unlikely to be more than palliative.

### Dietary Management

Although no literature exists on the long-term impact of diet on survival times, the management of any mature horse recovering from an acute episode of liver disease or an individual with confirmed hepatic insufficiency associated with chronic liver disease should include dietary measures. Intuitively, horses with liver disease should benefit from a high-carbohydrate, low-protein diet, with the protein component being proportionately higher in branched chain amino acids compared with aromatic amino acids. The latter distinction is particularly important if blood ammonia has been demonstrated to be elevated and the horse has signs of hepatic encephalopathy.

In addition to manipulating the individual feed components, it is valuable to offer small frequent feedings up

to four to six times a day to lessen the gluconeogenic load on the diseased liver. A ration composed of two parts beet pulp and one part cracked corn in molasses fed at a rate of 2.5 kg/100 kg body weight divided over multiple feedings has been suggested. Alfalfa and leguminous grasses/hays should be avoided because of their high protein component. Grass pasture is perhaps the best forage source because it presents a lower protein load on the liver compared with the legumes and encourages consistent intake, although the most lush fresh spring pastures obviously should be avoided. Grass and oat hays are palatable and appropriate alternatives for the horse with hepatic disease. Water-soluble vitamins such as vitamin B<sub>1</sub> and folic acid also may be administered. Fat-soluble vitamin (vitamins A, D, E, and K) supplementation is particularly appropriate for cholestatic diseases. Vitamin E supplementation (6000-8000 IU per adult q24h) is an appropriate adjunct therapy for its antioxidant properties in horses with inflammatory hepatitis/cholangiohepatitis.

Unfortunately, formulation of an appropriate diet to include micronutrient and vitamin supplementation is no guarantee of intake, and the biggest challenge often faced by owners of horses with severe liver disease is getting the horses to eat enough to maintain or improve their body weight. Frequently, either corticosteroids or anabolic steroids are considered as therapeutic adjuncts to improve appetite.

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# SECTION IV

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## Skin Diseases

*Edited by Dr. Stephen D. White*

### CHAPTER 4.1

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## Photosensitivity

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**P**hotodermatitis is a cutaneous reaction induced by exposure to light. Multiple normal reactions occur in the skin with ultraviolet radiation (UVR) exposure such as photodamage (sunburn; see Chapter 4.19). This chapter is devoted to photosensitivity, a disease state in which the skin has undergone a change because of a photosensitizer and is now sensitive to exposure to UVR. Phototoxicity and photoallergy are two forms of photosensitivity discussed here.

### ETIOLOGY

The amount of light, the wavelengths of the light, and the properties of the tissue exposed determine where and what type of damage occur in the skin when exposed to light. The amount of UV exposure to the skin varies with season, time of day, latitude, and altitude. UVR can be reflected up to 85% in water, snow, and sand, which yields a double exposure. The ultraviolet (UV) light spectrum is divided based on wavelength into UVC (200-290 nm), UVB (290-320 nm), and UVA (320-400 nm). The longer the wavelength is, the deeper the penetration into the skin. UVB penetrates the epidermis and upper dermis and UVA penetrates to the deep dermis. The shorter wavelengths are more biologically active. Therefore UVB is responsible for most damage to the epidermis and superficial dermis.

When a molecule absorbs energy from light, a biologic response can be initiated. This is called *photochemistry*. The molecule absorbing the light is the chromophore. Photosensitivity occurs when a chromophore acts as a photosensitizer and reacts with another molecule, which causes it to have a chemical change. Chromophores have specific light absorption spectrums. Melanin (a chromophore that serves in a protective, rather than a photosensitizing, role) has a broad absorption spectrum from less than 300 nm to 1200 nm. Melanin functions by absorbing and scattering UVR, which helps protect pigmented skin. Without pigment, the epidermal and dermal cells absorb the light energy and undergo deleterious changes.

Phototoxicity and photoallergy are cutaneous photosensitivity disorders associated with concomitant exposure to a photosensitizer and to UVR of the appropriate wavelength. Mechanisms for phototoxicity include (1) generation of reactive oxygen species that damage cellular membranes, (2) covalent binding to pyrimidine bases of DNA, and (3) release of inflammatory mediators such as histamine and eicosanoids. No immunologic mechanism is involved with phototoxic agents. Therefore multiple animals kept under suitable conditions are affected.

In photoallergy, a photoallergen must penetrate the skin and be processed by the immune system similar to atopic dermatitis. This is a photoactivated "allergic dermatitis." The typical photoallergen occurs only in previously sensitized animals. Eruption usually begins 24 to 72 hours after exposure to the allergen and sunlight. Many topical products used on horses may be the source of photoallergy. Fragrances and sunscreens have been the most frequently documented causes of photoallergy in humans (Box 4.1-1). Photoallergy may present as a pruritic dermatosis. The symptom of pruritus is used in human medicine to identify photoallergy, whereas phototoxicity usually is characterized by a burning sensation.

Photosensitizers may be exogenous in origin (from the environment) or endogenous (a byproduct of metabolism or disease). Exogenous agents may be ingested feed or pasture (Table 4.1-1). The classic example of an exogenous agent is hypericin. This photodynamic agent reaches the skin after being absorbed from the digestive tract in horses grazing pastures in which *Hypericum* spp. (St. John's wort) are growing. Most recognized cases of contact photosensitization have occurred from pastures containing clover. The etiologic agent in clover that sometimes produces a photodynamic agent is unknown. In the horse hepatic disease is the main cause of elevated levels of phyloerythrin, an endogenous photosensitizing agent. It is produced when bacteria in the intestine degrade chlorophyll. In the presence of hepatic disease or cholestasis, elevation of phyloerythrin levels occurs. Therefore photosensitivity

# BOX 4.1-1

## Contact Agents Associated with Photoallergy

### Antibacterials

Triclosan  
Clorhexidine

### Fragrances

Sandalwood oil

### Sunscreens

PABA  
PABA esters  
Benzophenones

### Therapeutic Agents

Diphenhydramine  
Chlorpromazine

PABA, Paraaminobenzoic acid.

# Table 4.1-1

## Exogenous Photodynamic Agents

Common Name	Scientific Name	Agent
St. John's wort	<i>Hypericum perforatum</i>	Hypericin
Buckwheat	<i>Polygonum fagopyrum</i>	Fagopyrin
Perennial rye grass	<i>Lolium perenne</i>	Perloine
Whiteheads, ranger's buttons	<i>Sphenocladium capitellatum</i>	Unknown
Spring parsley	<i>Cymopterus watsoni</i>	Psoralen
Bishop's weed	<i>Ammi majus</i>	Psoralen
Dutchman's breeches*	<i>Thamnosma texana</i>	Psoralen
Celery/parsnips infected with fungi		Phytoalexins

\*This entry does not refer to the Dutchman's breeches (*Dicentra cucullaria*) common to woodlands in the northeastern portions of the United States.

ity may be the initial clinical sign noted with hepatic dysfunction. Ingestion of plants that contain pyrrolizidine alkaloids (Table 4.1-2) is the most common cause of liver disease leading to photosensitization. Other less common causes are hepatotoxic drugs, toxins, fungi, and infectious agents, in addition to biliary calculi and cholangiohepatitis (Box 4.1-2). A congenital etiology for photosensitization such as the porphyrias reported in cattle has not yet been documented in the horse but should be considered with disease in the neonatal or juvenile horse.

An entity unique to the horse has been described and its clinical signs suggest a photo-activated etiology, although this has not been proven. It has been termed *pastern leukocytoclastic vasculitis*, *pastern leukocytoclastic vasculopathy*, and

# Table 4.1-2

## Plants with Pyrrolizidine Alkaloid

Common Name	Scientific Name
Common groundsel	<i>Senecio vulgaris</i>
Ragwort, stinking Willie	<i>Senecio jacobaea</i>
Fiddleneck	<i>Amsinckia intermedia</i>
Rattleweed	<i>Crotalaria</i> spp.
Salvation Jane	<i>Echium lycopsis</i>

# BOX 4.1-2

## Elevated Phylloerythrin Levels Not Associated with Alkaloids

### Infectious Agents

Leptospirosis  
Other infectious agents causing generalized hepatic damage

### Biliary Calculi

Cholestasis  
Cholangiohepatitis

### Mycotoxins

Sporidesmin from *Pithomyces chartarum*

### Toxins

Carbon tetrachloride  
Copper  
Phosphorus

### Congenital Varieties

Genetic defect of phylloerythrin transport (reported only in Corriedale lambs)

*pastern leukocytoclastic dermatitis*. The factors suggesting a photo-activated etiology include restriction of lesions to nonpigmented distal extremities in the majority of cases, and occurrence of the disease most commonly in the summer months in areas with abundant sunlight. However, the disease may have a more complicated etiology because it may occur in only one of several nonpigmented limbs or affect only one horse in a herd while others with nonpigmented extremities are unaffected. In addition, it has been noted that simple avoidance of sunlight is usually not sufficient to treat the disease.

## HISTORY

Collecting a complete history is important in cases suspected of having photosensitivity. The most common complaints are erythema, swelling, and pruritus, or in more severe cases vesiculation, open wounds and peeling of the skin. Veterinarians should inquire about the initial

appearance of the lesions and their location. An astute owner may have noticed the initial lesions of erythema and edema and noticed that they occurred mainly in the white skin areas. If the distribution is limited to the muzzle and distal extremities, concern should arise regarding the possibility of a contact photosensitizer. A history of occurrence is also important because a seasonal history affecting the nonpigmented areas may raise the suspicion of seasonal exposure to certain plants or the application of a photosensitizing agent such as a topically applied fly repellent or sunscreen as possible causative agents. Seasonality decreases concern about liver disease.

If the horse is pastured, the quality of the pasture should be evaluated, in particular for plants that are known photosensitizing agents or hepatotoxic agents. It should be determined if the horse has been exposed to moldy feedstuffs or environmental hepatotoxins such as copper, phosphorus, or carbon tetrachloride. Exposure to drugs, both systemic and topical, should be determined. If multiple horses are affected a contact or ingested photosensitizer or an infectious agent like *Dermatophilus congolensis* or dermatophytes (both of which have been anecdotally linked to photosensitivity) should be considered.

## CLINICAL SIGNS

The lesions associated with photosensitivity can vary tremendously. The lesions involve nonpigmented or lightly pigmented skin with a thinner hair coat. The distribution of lesions may depend on the type of photosensitizer. If it is due to contact with pasture plants or environmental sprays then the distribution affects the muzzle and distal extremities. Photosensitization resulting from topically applied products may have irregular patterns of distribution. In the case of endogenous photosensitizers all of the nonpigmented areas usually are involved and in severe cases pigmented areas also may be affected.

In the mild form photosensitivity can appear similar to sunburn or actinic dermatitis with erythema, edema, and scale. Moderate cases may include lichenification, serum exudation, and crusting with erosions and ulcers. Pruritus and/or pain also may be present. Finally in more severe cases, tissue necrosis and sloughing can occur. Because of the wide variety of lesions, photosensitivity should be a differential diagnosis whenever nonpigmented skin is involved especially if lesions seem to be well demarcated from pigmented skin. Systemic signs of hepatic disease also may be present. These include lethargy, anorexia, ventral edema, icterus, weight loss, and encephalopathy.

Depending on the history, distribution, and severity, multiple differential diagnoses exist. For milder lesions that appear erythematous and scaly, differentials should include actinic dermatitis, topical irritant, or dermatophytosis. If pruritus is present, allergic etiologies are included in the differential list. When signs affect mainly the distal extremities, pastern leukocytoclastic dermatitis and *Chorioptes equi* should be considered. Exudation and crusting should lead to consideration of infectious agents, especially *D. congolensis*, which has been reported to have well-demarcated lesions confined to nonpigmented skin. Immune-mediated diseases such as sarcoidosis, vasculitis, and drug eruptions should be considered as differentials.

## DIAGNOSIS

The history and clinical signs are the most important indicators for suspecting a photosensitivity. An inspection of the environment and feedstuffs for the presence of plants containing photodynamic agents or hepatotoxic agents such as pyrrolizidine alkaloids is helpful. All horses suspected of having a photosensitivity should have chemistry profiles and liver function profiles evaluated. Liver-specific enzymes that should be evaluated include sorbitol dehydrogenase, glutamate dehydrogenase, arginase, and  $\gamma$ -glutamyl transpeptidase. Other enzymes that may be elevated but are not specific to the liver include aspartate aminotransferase, lactate dehydrogenase, and alkaline phosphatase. Also of value are levels of bilirubin, lipoprotein, clotting factors, bile acids, and albumin. The erythrocytes should be examined for alkaloids to determine potential exposure to hepatotoxic plants. Phylloerythrin levels can be measured and should be less than 10  $\mu\text{g/dl}$  to evaluate liver disease not secondary to alkaloid exposure. If the results indicate hepatic disease, ultrasonography and biopsy allow for evaluation of cholelithiasis and megacystosis and fibrosis, respectively. This may help to determine the long-term prognosis.

Biopsy of the skin lesions and histopathology are often nonspecific but can help rule out other differentials. Histopathology from affected lesions may have apoptotic keratinocytes ("sunburn cells"), lymphocytic perivascular dermatitis, epidermal hyperplasia, and hyperkeratosis. Crust formation, erosion, ulceration, and necrosis may be present.

## THERAPY

Determination of the type of photosensitizing agent causing the problem is an important element in identification of the horse's long-term prognosis. The horse should be removed from sunlight while this assessment is occurring. Suspected drugs should be withdrawn. All dietary sources of pyrrolizidine alkaloids or other hepatotoxic plants must be removed from the diet. If contact photosensitivity is suspected the lesions should be washed. Whirlpools or soaks with mild antiseptics may help with secondary bacterial infections. Systemic antibiotics may be indicated with deeper lesions. Corticosteroids may be indicated to reduce inflammation. Prednisolone should be used instead of prednisone because liver metabolism may be a factor. Dosages of 1 mg/kg daily for 1 week then 0.5 mg/kg daily for the second week have been effective. If the horse has advanced liver disease this may affect the decision to pursue additional diagnostics and treatment (see Chapter 3.26: "Liver Disease") because the prognosis is poor. Without hepatic disease the prognosis is good to fair depending on the severity of signs and the ability to identify and avoid the agent.

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## CHAPTER 4.2

# Cutaneous Adverse Drug Reactions

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An adverse drug reaction (ADR) is as an undesirable effect that results from the administration of a drug. These reactions can be either immunologic or nonimmunologic. Mechanisms of immunologic ADRs include IgE-dependent mast cell degranulation (type I), antibody mediated cellular cytotoxicity (type II), deposition of immune complexes with initiation of the complement cascade (type III), and cell-mediated tissue damage (type IV). Combinations of these mechanisms may lead to drug-induced autoimmune diseases. Immunologic ADRs occur after previous administration of an offending drug or cross-reactive substances. Subsequent exposure or continuous treatment with the drug or related substances induces the immunologic reaction characterized by systemic and/or cutaneous lesions.

Type I hypersensitivities are induced by the cross-linking of mast cell-bound IgE by the drug or drug metabolite leading to mast cell degranulation. Binding of antibody to drug-related antigens on cell membranes (type II) leads to cell damage through the initiation of the complement cascade. Deposition of circulating immune complexes (type III) also activates the complement cascade. Delayed type hypersensitivities (type IV) are the result of T cells recognizing processed drug antigens on cell surfaces, which results in target cell lysis.

Examples of nonimmunologic ADRs are overdoses, cumulative toxicity, facultative effects (e.g., antibiotics that destroy normal bacterial flora and allow the growth of other bacteria or fungi), drug interactions, alteration in metabolic enzymes, alteration of metabolic status, teratogenicity, effects on spermatogenesis, anaphylactoid reaction (e.g., opiates release mast cell mediators), intolerances and idiosyncratic reactions. These nonimmunologic ADRs usually do not cause cutaneous reactions.

### CUTANEOUS REACTION PATTERNS

Cutaneous reaction patterns associated with ADR are pleomorphic and can mimic any skin disease. Therefore ADRs always should be included as a possible differential diagnosis. Most practitioners recognize urticaria as the most common equine ADR. Urticaria results from the degranulation of cutaneous mast cells. The mediators released from mast cells induce dilation of and leakage from vessels and act as chemoattractants for leukocytes. Physical examination findings and historical information are used primarily

to diagnose urticaria. A biopsy may confirm the diagnosis of urticaria when the lesions are firmer than expected or are chronic (longer than 8 weeks). A biopsy is needed to rule out other causes of urticaria-like lesions such as infections or erythema multiforme.

Erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) are cutaneous reaction patterns that can be induced by an adverse drug reaction, viral infection, bacterial infection, or a neoplasm. In humans and dogs, it has been shown that EM is associated less commonly with a drug reaction than SJS or TEN. SJS and TEN have not been described in the horse. EM is believed to be an immunologic disease in which the "programmed cell death," also known as *apoptosis*, is initiated by cell-mediated or unknown factors. The onset of clinical lesions is usually acute. Erythematous macules and papules develop into crusts, which may have an arciform appearance. Target lesions, circular lesions with central clearing that can resemble urticaria, are a hallmark of EM in humans and dogs. Less often, EM lesions may be plaque-like, vesicular, bullous, ulcers, or epidermal collarettes. Lesions are found usually on the trunk, but the mucocutaneous junctions, oral mucosa, and ears may be involved. In horses EM usually presents with urticarial-like lesions that are self-limiting and nonrecurring. Because the lesions can be so pleomorphic, clinical differentiation is often not possible and a definitive diagnosis may require a skin biopsy. Areas of erythema without crusting, erosions, or ulcerations are ideal sites for biopsy because an intact epidermis is needed to make the diagnosis. Multiple specimens increase the chance of obtaining a diagnosis.

Exfoliative dermatitis has been described as a diffuse scaling, crusting dermatitis with variable alopecia. This is an uncommon cutaneous reaction pattern associated with ADRs in humans. However, in a study of 19 horses with ADRs, it was the most common form of ADR seen (26.3% of cases). Trimethoprim-potentiated sulfonamides were the most commonly incriminated drug.

In horses, a systemic lupus erythematosus (SLE)-like syndrome has been described. The equine SLE-like syndrome differs from that described in humans and dogs in that it has cutaneous lesions compatible with discoid lupus erythematosus (DLE) and systemic signs compatible with SLE. These horses have a variably positive antinuclear antibody (ANA). Sharply demarcated areas of depigmentation around the eyes, lips, nostrils, and perineal regions

define cutaneous lesions. Systemic signs include polyarthritis, uveitis, hypopyon, hyphema, pyrexia, and weight loss. It is believed to result from the combination of genetic and immunologic predisposing factors with initiating "triggers." Possible triggers include infections, drugs, environmental factors, or stress. When an SLE-like syndrome is suspected, skin biopsies, blood for a complete blood count, chemistry panel and ANA, and urine for urinalysis should be submitted. Removal of the offending drug may resolve the lesions. However, drugs may induce a "true" autoimmune disease and lesions may persist after drug withdrawal. The latter condition may require treatment with immunosuppressive drugs.

Pemphigus foliaceus (PF) has been well described in the horse. Among other causes, drugs have been implicated in the initiation of PF. Drug-induced PF and PF-like drug reactions have been recognized. With drug-induced PF, the lesions persist after discontinuation of the offending agent, whereas with PF-like drug reactions, the lesions resolve with discontinuation of the drug. Biopsies are required to evaluate for morphologic lesions consistent with PF but cannot distinguish between "true" PF, drug-induced PF, and PF-like drug reaction. The distinction between these conditions is made based on history and clinical follow-up after drug withdrawal.

Fixed drug eruptions (FDE) have been described in humans and dogs, but the current authors were unable to find equine cases in the veterinary literature. Cutaneous FDEs are characterized by recurrence of skin lesions at the same site with each exposure to the offending drug. FDE can vary in severity from small focal lesions to generalized involvement.

Contact reactions have been reported in horses. A contact reaction should be suspected whenever a topical medication is used, and the lesions worsen or initial improvement is followed by recrudescence despite continued treatment. Some of these reactions may not be immunologic in nature but could be either irritant reactions or the result of inappropriate application. A skin biopsy may be useful to distinguish between the underlying dermatosis, for which the topical was prescribed, and an adverse contact reaction.

## SKIN BIOPSY

Skin biopsy is a useful tool in diagnosis of skin diseases. To improve the chances of obtaining a diagnostic sample, the biopsy should be taken without disturbing the epidermis. Therefore the area from which the biopsy is to be taken should not be scrubbed or shaved because these procedures alter the skin's surface. The hair coat may be lightly clipped before the sample is taken as long as the epidermis is not disturbed. Lidocaine 2% (0.5-1.0 ml) is injected subcutaneously at the site. The biopsy is obtained using a sterile biopsy punch (these authors prefer using a 6 mm or 8 mm disposable biopsy punch [Miltek Instruments, Bethpage, N.Y.]). Once the epidermis and dermis are cut by the punch, the sample should be lifted carefully by a small corner of a deep edge (with caution not to crush the sample) and cut loose with a pair of iris scissors. The sample should be placed immediately in formalin unless additional procedures such as immunohistology are

planned. For unusual cases the pathology service should be contacted before taking the biopsy. For larger lesions, a wedge resection is preferred following the same guidelines above. Biopsies should be taken from areas that have an intact epidermis if possible and from all areas that are clinically different. For example, if depigmented lesions, erythematous lesions, and crusted lesions are present, samples should be obtained from all three areas. The more samples submitted, the greater the chance of obtaining an accurate etiologic diagnosis.

## HISTOPATHOLOGY

The skin has a limited repertoire of mechanisms to respond to a large variety of insults. The inflammatory reaction patterns seen with immune-mediated ADRs are often pleomorphic and can be indistinguishable from other immune-mediated skin diseases. Morphologic changes therefore must be interpreted in the context of the clinical presentation of the horse and the history. To maximize the benefit of the biopsy, a complete history must be provided with the submission of the tissue sample.

### Urticaria

The lesions of urticaria include a variable degree of dermal edema associated with mild to severe superficial and deep dermatitis composed of primarily eosinophils, lymphocytes, and mast cells. Severe dermal edema may result in subepidermal vesiculation. The epidermis may appear normal or exhibit spongiosis and microvesiculation. In mild cases of acute urticaria, no obvious histologic changes occur because mild dermal edema might be removed during fixation of the tissue.

### Erythema Multiforme

Scattered single cell necrosis of keratinocytes (these are referred to as *apoptotic keratinocytes*) is found throughout the entire thickness of the epidermis and within the follicular epithelium. Small lymphocytes are present next to the apoptotic keratinocytes. This lymphocyte satellitosis, with CD8+ cytotoxic T cells, indicates an immune mediated process. Extensive single cell necrosis can result in coalescing epidermal necrosis with secondary vesiculation and ulceration. A perivascular superficial dermatitis with lymphocytes, macrophages, and neutrophils is usually present. Occasionally, this superficial inflammation expands to a diffuse superficial, bandlike, or lichenoid dermatitis, which may develop into an interface dermatitis with obscured dermal-epidermal junction, basal cell degeneration, and vacuolization of the basement membrane zone.

### Stevens-Johnson Syndrome

Histologic lesions identical to erythema multiforme characterize SJS. TEN is accompanied by a coalescing epidermal necrosis induced by massive apoptosis in absence of primary dermal inflammatory changes. Subepidermal vesiculation develops as a result of basal cell damage. In humans, scattered cytotoxic T cells can be demonstrated

among the apoptotic keratinocytes by immunohistology. SJS and TEN have not been documented in horses.

### Exfoliative Dermatitis

In humans this is characterized by a nondiagnostic subacute to chronic hyperplastic dermatitis. Acanthosis, orthokeratotic hyperkeratosis, and increased rete peg formation are accompanied by a perivascular lymphocytic, plasmacytic and histiocytic dermatitis. Parakeratosis may be seen at an early stage. Of the horses that were reported with exfoliative dermatitis, three had variable degrees of predominantly lymphocytic, perivascular-to-interstitial dermatitis, and orthokeratotic to parakeratotic hyperkeratosis. One horse had an epitheliotropic lymphocytic infiltrate in addition to multinucleated histiocytic giant cells within the superficial dermis. One other horse had a few papillary microabscesses composed primarily of neutrophils.

### Pemphigus Foliaceus

Drug-induced PF and PF-like drug reactions are histologically indistinguishable. Intraepidermal and subcorneal pustules with nondegenerative neutrophils and acantholytic keratinocytes are transient. More often, the nondegenerative neutrophils and acantholytic cells are found in the large layered crusts covering several follicular openings. Variable degrees of perivascular, mononuclear dermatitis are present and subepidermal edema may occur.

### Lupus-Erythematosus–Like Drug Eruptions

These present with interface dermatitis. Cell-poor interface dermatitis is characterized by vacuolar degeneration of basal cells, vacuolization of the basement membrane zone, and minimal lymphocytic exocytosis. Cell-rich interface dermatitis, also referred to as *lichenoid interface dermatitis*, is characterized by a marked lymphocytic and plasma cell infiltrate obscuring the dermal-epidermal junction in addition to the basal cell changes. Pigmentary incontinence into the dermis occurs, and subepidermal vesiculation may occur subsequent to the damage of the basal cells and alteration of the basement membrane zone.

### Vasculitis

Well-circumscribed, small, punched-out dermal and epidermal areas of coagulation necrosis (clinically referred to as “punched-out” necroses), microhemorrhage, protein rich edema, and fibrin deposition are features of vascular damage. Fibrinoid necrosis, thickening, edema, and hyalinization of vascular walls are associated with a variable degree of inflammatory infiltrate tightly surrounding and infiltrating dermal vessels. Leukocytoclasia, characterized by the presence of degenerative intramural leukocytes, is transient and is often no longer present at the time of biopsy sampling. More commonly, a pleocellular infiltrate composed of histiocytes, lymphocytes, and fewer neutrophils within the vascular walls and surrounding vessels of different size is seen. Occasional intravascular thrombi can be observed. At a subacute stage, wispy dermal fibrosis and deposition of homogenized collagen dis-

sect preexisting collagen bundles. The latter indicates low-grade ischemia of the dermis.

### Drug Reactions with Mixed Histopathologic Features

Drug reactions may result in histologic lesions characteristic of several different immune-mediated diseases. A vascular component is often associated with other patterns. Leukocytoclastic and nonleukocytoclastic, granulomatous vasculitis may be accompanied by an interface dermatitis or intraepidermal vesiculation and pustulation with acantholysis.

### Contact Dermatitis

Irritant contact dermatitis is characterized by variable degrees of epidermal necrosis, spongiosis, and exocytosis. As a result, the epidermis becomes hyperplastic and parakeratosis develops. The epidermal lesions are accompanied by a perivascular dermatitis, which may progress to diffuse and pleocellular dermatitis secondary to erosions and ulcerations.

### INCIDENCE OF ADVERSE DRUG REACTIONS IN THE HORSE

The exact incidence of ADRs in horses is not known. In one report, the incidence was 9.8% of all equine cases examined by the dermatology service. This incidence appears high compared with the reported ADRs in dogs (2%) and cats (1.6%). In humans spontaneous reporting of ADR only identifies 1 in 20 cases. The FDA estimates that only 1% of ADRs are reported, so the reported incidences of ADRs may be too low. Additionally, confirming a diagnosis of an ADR requires challenge with the offending drug. Because many ADRs are severe and may be life threatening, this is not medically or ethically prudent. Therefore many reports of ADRs may be anecdotal and unconfirmed. In humans the most frequent offenders are antibiotics and nonsteroidal antiinflammatory agents.

A review of the literature shows few reports of adverse drug reactions in the horse and even fewer of cutaneous reactions (Table 4.2-1). As with humans, antimicrobial agents and more specifically penicillins are the most frequent causes of ADRs.

### MANAGEMENT OF ADVERSE DRUG REACTIONS

The treatment of ADRs involves immediately discontinuing the offending drug(s). If an ADR is suspected, these authors recommend discontinuing all drugs, herbal remedies, and supplements that the horse has been receiving. The time period required for resolution of clinical signs is dependent upon the half-life of the offending drug. Additionally, enhancing the elimination of the drug may lead to quicker improvement. If other therapeutics are required to treat the underlying disease and/or the ADR, drugs unrelated to any previously administered compounds should be chosen. Although controversial, corticosteroids may be considered in the treatment of adverse drug reactions.

Table 4.2-1  
Reported Adverse Drug Reactions in Horses

Journal	Antibiotics	Nonsteroidal Antiinflammatory Drugs	Anesthetics/ Sedatives	Analgesics	Miscellaneous Drugs	Vaccines
Gray et al 1990 <sup>a</sup>	12			6		4
Maddison 1992 <sup>b</sup>	3					
Maddison 1994 <sup>c</sup>	2	2		1		
Maddison 1996 <sup>d</sup>	4		4		5 (2)	
Tjalve 1997 <sup>e</sup>	28	8	6		9 (6)	10
Scott and Miller 1997 <sup>f</sup>	10 (10)	2 (2)	2 (2)		8 (8)	

<sup>a</sup>Gray A, Evans C, Kidd A: Suspected adverse drug reactions to medicines during 1989. *Vet Rec* 1990; 21:376-378.

<sup>b</sup>Maddison J: Adverse drug reactions: report of the Australian Veterinary Association Adverse Drug Reaction Subcommittee, 1992. *Aust Vet J* 1992; 69:288-291.

<sup>c</sup>Maddison J: Adverse drug reactions: report of the Australian Veterinary Association Adverse Drug Reaction Subcommittee, 1993. *Aust Vet J* 1994; 71:53-56.

<sup>d</sup>Maddison J: Adverse drug reactions: Report of the Australian Veterinary Association Adverse Drug Reaction Subcommittee, 1994. *Aust Vet J* 1996; 73:132-136.

<sup>e</sup>Tjalve H: Adverse reactions to veterinary drugs reported in Sweden during 1991-1995. *J Vet Pharmacol Ther* 1997; 20(2):105-110.

<sup>f</sup>Scott DW, Miller WH: Idiosyncratic cutaneous adverse drug reactions in the horse: literature review and report of 19 cases (1990-1996). *Equine Pract* 1997; 19(12):12-18.

Numbers in parentheses indicate the number of adverse reactions that had cutaneous signs. For example, 5(2)—of five adverse drug reactions, two had cutaneous signs.

The following guidelines have been established to reduce the incidence of ADRs in humans: (1) charting of all medications, (2) using the oral route over intravenous or intramuscular whenever possible, (3) reporting all suspected drug reactions and (4) maintaining a high level of suspicion.

To improve understanding of ADRs in the horse, veterinarians need to improve the reporting and publishing of ADRs. In addition, the clinician must remember that ADRs may be caused by drugs, herbal remedies, and supplements obtained over the counter (without a prescription).

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## CHAPTER 4.3

# Atopy

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**A**topy is a genetic, dermatologic, and/or respiratory condition that occurs when a horse develops sensitizing antibodies to environmental allergens such as molds, grasses, trees, weeds, fabrics, and dust. The sensitizing antibody that is produced, immunoglobulin E (IgE), causes cross-linkage on mast cells within the affected tissue. This cross-linkage results in the release of inflammatory mediators such as leukotrienes and prostaglandins. The end result is inflammation of the skin and/or respiratory system and discomfort for the affected horse.

Arabian and Thoroughbred horses appear to be predisposed to developing atopy. This finding supports the idea that atopy is an inherited condition in horses; however, the exact mode of inheritance remains unknown. One stallion has been documented to have atopy and sire five offspring with atopy, and in each breeding the mare was different. This finding suggests the possibility of a dominant inherited trait for equine atopy. More studies need to be performed to prove or disprove this theory.

Not all horses with atopy have allergies to the same allergens. It is therefore important to have some method by which offending allergens are identified so that they can be prevented and/or the horse can be managed through hyposensitization treatment. Over the years, intradermal allergy testing and serum allergy testing have been developed and used to identify potential offending allergens. As with any test, false-positive and false-negative reactions can occur and can make interpretation difficult. The clinician must be familiar with the limitations and advantages of each test. Interpretation requires that the veterinarian correlate the history with clinical signs and pollination times of the various allergens. Once the veterinarian has this information, a proper recommendation for treatment may be made.

### HISTORY

Most horses with atopy have a seasonal skin and/or respiratory problem. Reports of horses with nonseasonal problems exist, but this occurrence is atypical. When a nonseasonal history exists, the horse usually has an allergy to molds or dust. Mold allergies usually cause clinical signs throughout the year but tend to be worse in the spring and fall.

Horses with atopic dermatitis usually have a history of pruritus, but an owner who does not spend a lot of time with the horse may miss this sign. Some horses with urticaria also may not be pruritic. Therefore the history of pruritus is not always helpful in the determination of whether an urticarial horse is atopic.

The clinical signs for equine atopy usually develop at a young age—1½ to 4 years old. It is important to remember that movement of the horse may play an important role in determining the age at which atopy develops. A horse that has lived 5 or more years in one geographic area without atopy may develop signs after moving to a different geographic area.

### CLINICAL SIGNS

A variety of clinical signs reportedly have been associated with equine atopy. The most common sign is pruritic dermatitis. The lesions include excoriations, alopecia, lichenification, and hyperpigmentation. Primary skin lesions (papules, pustules) rarely occur. As previously described, some horses have chronic recurrent urticaria that may or may not be pruritic. The dermatologic lesions are usually found on the face, ear, ventrum, and legs. Some horses with atopy look similar to horses with insect hypersensitivity.

Horses with heaves and atopy may have clinical signs that are no different than those in horses with heaves not associated with atopy. These signs can include head-tossing, snorting, coughing (especially dry, unproductive coughs), bilateral mucopurulent discharge in the nostrils, runny eyes, stomping, rubbing the nose and eye on the front leg or on an object in the environment, labored breathing, and exercise intolerance.

### DIFFERENTIAL DIAGNOSES

Differential diagnoses for pruritic atopic dermatitis include insect hypersensitivity, food allergies, and contact hypersensitivity. Insect hypersensitivity is the most common. Differential diagnoses for horses with respiratory problems include upper respiratory infection (viral, bacterial, fungal), congestive heart failure, and bronchitis.

### DIAGNOSTIC TESTS

#### Atopic Dermatitis

Several tests can be performed if a clinician suspects a horse has atopic dermatitis. Skin biopsy shows a superficial-to-deep perivascular dermatitis with eosinophilia. This type of reaction pattern is not specific for atopy and may be seen with other types of allergies.

Other diagnostic tests, including an intradermal allergy test or a serum allergy test, can help to identify potential offending allergens but do not, however, diagnose atopy. This diagnosis must be based on a compatible history,



clinical signs, and elimination of other differential diagnoses. Of the two tests, the intradermal allergy test appears to be the more sensitive and better test to identify potential sensitizing allergens in a horse. However, this test is not without its limitations, including false-positive and false-negative results.

#### **Intradermal Allergy Test**

Most clinicians sedate horses with xylazine (0.05 mg/kg IV) when they perform intradermal allergy testing. A rectangular area (30 × 15 cm) on the lateral aspect of the neck is clipped with a number 40 blade. Dots spaced approximately 2 to 5 cm apart in permanent marker identify the locations where allergens will be injected. A volume of either 0.5 or 1.0 ml of the diluted aqueous allergen is injected intradermally. Although this author prefers a volume of 1.0 ml, the exact volume does not matter as long as it is the same volume of allergen at each site. Positive and negative controls are injected at the beginning and the end of the skin test. The positive control consists of a commercially prepared solution of histamine diluted to a concentration of 1:100,000 weight to volume. Saline (0.9% NaCl solution) or sterile water serves as the negative control. The reactions are read at set time intervals; the author prefers 15 minutes, 30 minutes, 4 to 6 hours, and 24 hours after allergen injection. The reactions are graded by comparison with the controls; a 4+ reaction is similar to the positive control, whereas a 0 reaction is similar to the negative control. Size, shape, turgidity, and presence of erythema are the subjective determinations used to evaluate skin test reactions. Reactions that are greater than or equal to a 2+ reaction are considered potentially significant. Allergens that produce positive reactions at more than one reading period are probably more significant than allergens that react slightly at only one time.

The history and clinical signs should be correlated with the results of the skin tests. Certain allergens (alfalfa, corn, cornsmut, grain mill dust, grain smut, black ant, mosquitoes, *Culicoides* organisms, fireant, *Rhizopus* organisms, *Penicillium* organisms, sheep wool epithelium, English plantain, red mulberry, black willow, mesquite, and dock sorrel) tend to cause false-positive reactions because they may be irritating when injected intradermally. In these cases a dilution of less than 1:1000 weight to volume or several injections at several different dilutions may need to be performed. Companies that sell allergens are familiar with—and can help the veterinarian to determine—the appropriate dilutions for skin testing. These companies can also help provide a source to obtain information on pollination times for the various allergens.

False-positive reactions have been reported in non-atopic horses with chronic laminitis and musculoskeletal disease. These horses may have hypersensitive immune systems and thus tend to react more to allergens. Normally these positive reactions occur in response to the irritating allergens. If a positive reaction does not correlate well with the clinical history and physical examination, then it probably is not clinically significant.

Some drugs, especially antihistamines and corticosteroids, can interfere with skin test results. Drugs such as acepromazine that affect vasodilation can also affect the

test results. If these types of drugs are not withdrawn for an appropriate length of time, false-negative skin test results will occur. This problem is usually obvious by the fact the histamine positive control does not react normally. Usually 0.1 ml of histamine creates a wheal 10 to 15 mm in diameter. Drug withdrawal times for horses should be similar to those used in small animals. Long-acting injectable steroids should not be administered for 3 months before skin testing. Oral steroids or injectable dexamethasone should not be given for at least 1 month before skin testing. Antihistamines should not be administered for a 7- to 10-day period before skin testing. If the horse's clinical signs are severe, this drug withdrawal period can be difficult to implement, in which case it may be more advisable to skin-test at the end of allergy season. Even so, some owners refuse to take their horses off medications, and others also object to sedation and clipping of their horses. In these cases, intradermal allergy testing is not an option.

Most concentrated solutions of allergens are useable for 6 to 12 months. Prediluted allergen solutions have a shelf life of approximately 1 month. Although purchasing the concentrated solutions and making the dilutions oneself is more cost-effective, the cost of concentrated allergen solutions for most regional allergy screens is several thousand dollars. The shelf life and cost usually make intradermal skin testing cost-prohibitive for the general practitioner. For this reason and because the results of skin testing are not always easy to interpret, a board-certified veterinary dermatologist or a veterinarian who performs multiple skin tests per week should perform the skin tests.

#### **Serum Allergy Testing**

Controversy exists regarding the usefulness of the serum allergy tests in horses. Lack of repeatability of test results and sensitivity of serum allergy blood tests are problems. In a recent study, three different serum allergy tests were compared with intradermal allergy test results. These tests were an enzyme-linked immunosorbent assay (ELISA) that uses polyclonal antiequine IgE, a radioimmunosorbent assay (RIA) in which the sample was treated to minimize nonspecific IgE binding, and an ELISA test that uses the Fcε receptor immunoglobulin E chain for IgE. None of the three serum allergy tests reliably detected allergen hypersensitivity in comparison with intradermal test results.

Despite the questionable efficacy of serum allergy testing in horses, anecdotal reports that some horses are benefited by hyposensitization based on the serum allergy blood tests exist. More studies need to be performed to adequately evaluate this situation.

## **TREATMENT**

### **Atopic Dermatitis**

Corticosteroids, antihistamines, and essential fatty acids are the three main groups of drugs used for antipruritic treatment in the atopic horse. Prednisolone can be administered at 0.5 to 1.5 mg/kg every 24 hours for 4 to 14 days, depending on the severity of the problem. This treatment is followed by a maintenance dose of 0.2 to 0.5 mg/kg every 48 hours. Alternatively, either oral or in-

jectable dexamethasone may be used. The initial dose of dexamethasone is 0.01 to 0.02 mg/kg every 24 hours for 4 to 7 days, followed by a maintenance dose of .01 to .02 mg/kg every 48 hours. Side effects associated with steroid use include polyuria, polydipsia, increased susceptibility to infection, mood changes, elevations in liver enzymes, and laminitis. The major predisposing factor for development of laminitis is a previous history of laminitis or predisposing hoof conformation, such as small feet on a large horse.

Antihistamines competitively inhibit the histamine H<sub>1</sub> receptor on the cell surface and thereby prevent the action of histamine on the cell. Antihistamines do not inactivate histamine or prevent its release. Several different antihistamines are available. Hydroxyzine hydrochloride is the first choice of most veterinary dermatologists. The dose ranges from 200 mg to 400 mg every 24 hours (PO or IM) to 1.5 mg/kg every 8 to 12 hours. This author's second-choice antihistamine is chlorpheniramine maleate (200 mg q12h PO regardless of body weight). Doses of 0.25 mg/kg every 12 hours have also been reported to be successful. Two other antihistamines that have been reported as effective are diphenhydramine hydrochloride (0.75 to 1 mg/kg q12h PO) and pyrilamine maleate (1 mg/kg q12h IV). Doxepin hydrochloride, a tricyclic antidepressant with antihistaminic properties, has also been used in horses at a dose of 300 to 400 mg every 12 hours or 0.5 to 0.75 mg/kg every 12 hours with varied success.

Side effects associated with antihistamine administration include sedation or behavior changes. The drug withdrawal period recommended by the American Quarter Horse Association for antihistamines is 10 days before the sporting event.

Essential fatty acids shift the arachidonic acid cascade away from production of proinflammatory mediators. This author has had the best experience with Derm Caps (DVM Pharmaceuticals, Miami, Fla.). The dose of Derm Caps ES for the average-sized horse is 5 capsules every 12 hours, whereas the dose for Derm Caps 100 is two to three capsules every 12 hours. As with any fatty acid, loose stools are a potential complication of this medication. If the horse develops loose stools after taking fatty acids, the next dose should be omitted and subsequent doses reduced by one capsule to see whether the horse tolerates the new dose. Hydroxyzine may be more effective when combined with the fatty acid treatment because fatty acids and antihistamines have a synergistic effect on pruritus in small animals. Derm Caps have two problems—cost and the capsule form. Most owners open the fatty acid capsule and sprinkle the contents on the grain. For most horses, palatability does not appear to be a problem.

Topical products may also relieve pruritus. Some ingredients that appear to be especially useful in horses are oatmeal, pramoxine, and hydrocortisone. Various combinations of these three ingredients are available commercially.

Hyposensitization therapy desensitizes the horse to al-

lergens that are suspected of causing the allergic signs. The exact mechanism of action is unknown, but the current thought is that allergy vaccines stimulate Th1 cells to produce and release interferon (IFN)- $\gamma$ . This IFN- $\gamma$  blocks the stimulation of IgE antibody synthesis by IL-4 from Th2 cells. Reported response to therapy varies from 60% to 80%, which is similar to reports in other species of animals. The side effects of hyposensitization therapy are minimal. Some animals develop swelling at the injection site, especially when the injection administered is the more concentrated allergen solutions. Anaphylaxis is rare.

Different allergy companies and different dermatologists use different vaccine schedules, which may explain some of the variability in response to the hyposensitization therapy. The usual vaccine maintenance schedule is 1 ml of a 20,000 protein unit (PNU) per ml of aqueous suspension of allergen administered every 7 to 21 days. The frequency of the vaccine administration depends on the horse's response to therapy.

## PROGNOSIS

Because equine atopy is an inherited condition, horses with this problem will have atopy for the rest of their lives. The owners of these horses need to be made aware that the horse will never be "cured." Instead, the owners must commit to treating and managing their horses' allergies on a long-term basis. The owners need to be aware of this situation before any treatment is instituted. With proper management, most horses can lead happy and productive lives.

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## CHAPTER 4.4

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# Arthropod Hypersensitivity

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Insect hypersensitivities are one of the major causes of pruritus and urticarial reactions in horses. Depending on the type of sensitivity and the severity, horses may exhibit seasonal signs or show signs year-round. The majority of insect hypersensitivities occur due to salivary antigens of biting insects. The most frequently involved insects are *Culicoides* spp., *Simulium* spp., *Haematobia irritans*, *Stomoxys calcitrans*, horse and deer flies, and mosquitoes. In addition to the occurrence of skin disease, some horses may exhibit signs of airway disease in response to insect allergens. Some of the latter reactions can occur in response to the previously mentioned biting insects, as well as to nonbiting arthropods such as house dust, forage, or straw mites. This occurrence is most likely due to aerosolized environmental insect allergens. Clinically, insect hypersensitivities exhibit familial tendencies; therefore a genetic predilection is suspected. Many cases become more severe as the horse ages.

Insect hypersensitivities are thought to be type I hypersensitivities, which are mediated by immunoglobulin E (IgE). When a specific antigen cross-links the IgE that is bound to mast cells in the skin and respiratory tract, they degranulate and release inflammatory mediators that cause the clinical signs. Delayed hypersensitivities may also be involved in the pathogenesis of insect hypersensitivities.

### ***Culicoides* HYPERSENSITIVITY**

The best-documented insect hypersensitivity is that caused by *Culicoides* spp. These insects—also known as “no-see-ums,” “biting midges,” and “punkies”—inflict an extremely painful bite due to their chewing mouthparts. They create primary papules, or wheals. Secondary lesions are a result of intense pruritus that leads to alopecia, scaling, crusting, hyperpigmentation, and lichenification. Lesions can occur on the dorsal and ventral aspect of the body. Mane and tail hairs are commonly broken and rubbed off.

*Culicoides* spp. are more active during warm weather, when there is little wind, and they typically feed at sunrise and sunset. This hypersensitivity is a worldwide problem, and the inciting *Culicoides* spp. depends on the geographic location. In some horses only specific species cause the problem, whereas in others, multiple species can elicit the clinical signs. Each species has specific feeding sites on the body that can be correlated with the site of clinical disease. Specific major histocompatibility complexes may be involved with this hypersensitivity. This author and others also have seen some horses and mules with skin disease and concurrent signs of airway disease with positive reactions to *Culicoides* spp. Most of these cases also had concurrent mold and pollen reactions.

### **Diagnosis**

Diagnosis is based on history, physical findings, intradermal skin testing, and response to fly control. Intradermal testing has been used extensively to identify the offending antigen, and a commercial antigen is likely to be available in the near future (Greer Laboratories, Lenoir, N.C.). This author and others from different regions have shown a very high correlation between clinical signs and the response to an antigen prepared from *Culicoides variipennis*, suggesting that a common major allergen is shared by multiple *Culicoides* spp. The diagnostic and therapeutic value of *in vitro* testing for *Culicoides* spp. and other insect hypersensitivities is very controversial. This author has not had the same clinical correlation with *in vitro* testing as with intradermal skin testing.

Often practitioners cannot practically maintain (because of financial reasons) the multiple insects' extracts necessary to perform intradermal testing themselves. Even when specialists are available to perform the tests, problems with false-positive and false-negative reactions can occur. These reactions can be minimized by the expertise of the allergist. Intradermal testing usually requires light sedation of the horse, but many horses may tolerate testing without sedation if the number of antigens is limited. The horse must not receive antihistamines for several days before the test. No oral glucocorticoids should be given for 7 to 14 days before testing, depending on the previously used steroid and duration of its use. Testing should be tailored to specific geographic regions as much as possible. Insect allergens that are known to be in the geographic area of the horse are recommended.

Once antigen selection has been made, allergenic extracts should be bought from a reputable supply company, such as Greer Laboratories in Lenoir, N.C. The standard concentration of most allergens for testing is 1000 protein nitrogen units/ml, or PNU/ml. Some allergens need to be tested at lower dilutions, and many insects are tested at two different dilutions to determine relative sensitivities of a reactive horse. Some allergens are also supplied in a weight to volume (w/v) format and require alternative dilutions. Dilution schedules can be obtained from the allergen supply company. Solutions for skin testing should be made up fresh every 4 weeks to maintain the appropriate potency.

The best site for testing is the lateral cervical region above the jugular furrow, between the jaw and the shoulder. The test area should not include the mane, as the skin is thicker and more difficult to inject in this location. The site should be clipped with a number 40 blade, and sites should be ink-marked for antigen identification. Approximately 0.05 to 0.1 ml of the antigen is injected intradermally. Injections

should be made 2 cm apart to avoid overlapping of reactions and misinterpretation of results. Reactions should be evaluated at 15 to 30 minutes, and if possible, at 45 minutes, 4 to 6 hours, and 24 to 48 hours. This frequency of evaluation may be impractical in many clinical situations. Owners can be advised to observe for late-onset or delayed reactions (swellings) and can measure these and report them to the clinician via telephone. Reactions are subjectively interpreted on a scale of 0 to 4 similar to that used for intradermal skin testing in small animals. Grading is based on size comparisons to a positive control (histamine 1:100,000 dilution) and a negative control (saline).

Skin biopsy can help support a diagnosis of insect hypersensitivity but often is not overly valuable, as many horses allergic to antigens not derived from *Culicoides* spp. exhibit similar histopathologic findings. The superficial mixed eosinophilic dermatitis can be seen with many types of insect hypersensitivities and other allergic dermatitis conditions. Secondary pyoderma or collagenolytic granulomas and eosinophilic folliculitis can also be seen in subsets of insect allergic horses.

## Treatment

Fly control both aids in the diagnosis of insect hypersensitivity and serves as a valuable treatment option. For insect control, a spray or wipe-on permethrin-based product works best. These can be applied daily in late afternoon. Pour-on permethrin 4% 1 to 3 times a week can also be effective. Braiding cattle ear tags that contain pyrethrins into the mane and tail can also work in some cases. Bath oil sprays (e.g., Skin-So-Soft, Avon Products, Inc.) can help when diluted 50:50 with water. Moving sensitive horses away from standing water and using screened stalls and fans can also be beneficial. In addition to avoidance, other treatment options rely more on systemic therapy, such as antihistamines, fatty acids, hyposensitization, and corticosteroids.

Antihistamines are classically defined as chemicals that block the action of histamines at receptor sites. However, they may also have antipruritic effects and reduce urticarial reactions by stabilizing mast cells and having antiserotonin properties. Many practitioners use these drugs even though the exact dosing regimen and pharmacokinetics are undefined in the horse. Antihistamines typically have fewer side effects than corticosteroids but are not nearly as effective for pure insect allergic hypersensitivities. This author's favorite antihistamine is hydroxyzine hydrochloride (1-1.5 mg/kg q8h IM or PO), a drug that is more effective for urticaria than pruritus. Pyrilamine maleate can be given parenterally at a dose of 1 mg/kg (q12h IM or slowly IV). Other antihistamines used with limited success include diphenhydramine HCl (0.75-1 mg/kg q12h IV or IM), doxepin hydrochloride (0.5-0.75 mg/kg q12h PO), and chlorpheniramine maleate (0.25 mg/kg q12h PO). Side effects are minimal and include light sedation, although occasional personality changes may be seen that may require reduction of dosages or discontinuation of the drug. The American Quarter Horse Association recommends a 10-day withdrawal of antihistamines before any shows or competition.

Fatty acid supplementation is increasingly used in the horse. Its goal is to modify the arachidonic acid cascade and thereby reduce the pruritus and urticaria associated

with inflammatory mediators from this cascade. In one study, 14 horses with seasonal *Culicoides* hypersensitivity were given 20 g daily of evening primrose oil and cold-water marine fish oil in an 80:20 ratio. Four horses showed no improvement; 5 horses improved; and 5 horses were much improved. In a more recent study at the University of Florida, 17 horses that were fed 200 ml of linseed per day for a 6-week period showed no significant change in pruritus or lesion surface areas. However, this time frame may have been too short to completely evaluate the potential benefits of omega-3 fatty acids. This author has had limited success using similar fatty acid combinations. An occasional horse may respond to the small animal Derm Caps 100s (2 to 3 capsules q12h; DVM Pharmaceuticals, Miami, Fla.). The author usually uses these fatty acids as an adjunct to other forms of therapy.

One of the most exciting areas for treatment of equine insect allergic skin disease is hyposensitization. Numerous studies now demonstrate its value for desensitizing horses to both insect and environmental allergens. Some studies show that approximately 60% of the horses have good to excellent responses to hyposensitization. In one study with only *Culicoides*-hypersensitive horses, 9 of 10 horses demonstrated significant improvement within 3 to 4 months of therapy. However, other cases may require longer periods of treatment to note positive results. In a placebo-controlled study by this author, 64% of the horses treated with hyposensitization showed a 50% or greater improvement, in comparison with only 23% with placebo. These cases included both insect- and pollen-reactive horses. The author prefers hyposensitization based on intradermal skin testing, although anecdotal reports suggest that hyposensitization based on *in vitro* allergy testing may also have value. The technique is similar to that used in small animals.

As in small animals, antigen volume and injection interval adjustments need to be made for each patient. Most horses require antigen booster injections at 7- to 14-day intervals, with volumes ranging from 0.5 to 1 ml. Injections are given subcutaneously over the lateral cervical area. Antigen reactions are uncommon, with swelling at injection sites being the most common. These generally resolve within 1 to 2 days.

Systemic glucocorticoids are often required to treat many allergic skin disorders. Making an accurate diagnosis before beginning glucocorticoid therapy is essential. Therapeutic dosages of glucocorticoids for treatment of equine dermatoses have not been determined, and each case must be treated individually. Recommended dosages are merely guidelines to follow. This author relies primarily on prednisolone and dexamethasone. Prednisone had previously been considered equivalent to prednisolone. However, new data suggest that some horses may not readily convert prednisone to its active metabolite, prednisolone. As a result of this research, the author now uses prednisolone instead of prednisone in the horse.

Depending on the severity of the case, dosages of glucocorticoids may need to be at the high or low end of antiinflammatory levels to control allergic hypersensitivity conditions. Treatment begins with a high dose for 7 to 14 days, followed by a tapering of the dose over 2 to 5 weeks, and then a maintenance period that may be used for as short a time as a few months or indefinitely, depending on the severity of the case and its seasonality. The high

dose for prednisolone is 0.5 to 1.5 mg/kg per day with maintenance dosages at 0.2 to 0.5 mg/kg every 48 hours. Some cases are resistant to prednisolone and may respond to either injectable or oral dexamethasone. The initial loading dose of dexamethasone is 0.02 to 0.1 mg/kg once daily, which may be followed by an oral maintenance dosage of 0.01 to 0.02 mg/kg every 48 to 72 hours. This regime is particularly helpful in more refractory cases. Writing out the induction and daily tapering and maintenance dosages is extremely valuable with oral glucocorticoids. Such a schedule permits safer administration at a "threshold dose" so that the case remains well-controlled.

## BLACK FLY DERMATITIS

Black fly dermatitis is caused by reactions to bites from flies in the family Simuliidae. As with *Culicoides* spp., these flies are active in the morning and evening and are more common in the spring and summer. They prefer to breed along rapidly moving water and can fly several miles from their breeding source. In addition to causing hypersensitivity due to salivary antigens, black flies also have a salivary toxin that increases capillary permeability and often creates a hemorrhagic crust at the site of a bite. In large numbers, black fly bites can create cardiorespiratory problems, shock, and even death. Primary lesions include painful papules and wheals. Pruritus creates similar secondary lesions as seen with *Culicoides* hypersensitivity. Lesions can be found in the ears, jaw, face, ventral abdomen and groin and on medial aspects of forelegs and thighs. These flies also have been associated with aural plaques on the medial aspect of the pinnae. It is thought that the black flies serve as a vector for papillomavirus and that aural plaques are a result of the papillomavirus and not the bite from the black fly.

Diagnosis and treatment are similar to that described for *Culicoides* hypersensitivity. Intradermal skin test antigen is available for testing and hyposensitization. Some insect-allergic horses can have cross-reactivity between simuliids and other insects. This fact needs to be considered when intradermal testing is performed. Some specialists question the value of simuliid antigen as a diagnostic test and its effectiveness for hyposensitization.

## HORN FLIES

Horn flies (*H. irritans*) are responsible for focal ventral midline dermatitis in horses—a seasonal dermatitis that occurs in the summer. It is a well-demarcated dermatitis usually in the umbilical area. These flies require fresh cattle feces to lay eggs. Separating horses from cattle helps reduce exposure to these flies. Applying residual insecticides to the affected areas is also a recommended form of treatment.

## STABLE FLIES

Stable flies (*S. calcitrans*) can create pruritic and painful papules and wheals. Multiple small collagenolytic granulomas have also been associated with stable fly-bite hypersensitivity. Stable flies tend to be seasonally most active in the summer and fall. They lay their eggs in manure or moist, decaying vegetation. The pruritus can induce sec-

ondary lesions of alopecia, scaling, crusting, and lichenification. The most commonly affected sites are the neck, back, chest inguinal region, and legs. Diagnosis and treatment is similar to other insect hypersensitivities. Commercial antigen is available for testing and hyposensitization. Stable flies can accumulate on shade trees during the heat of the day; thus spraying trees with insecticide can be helpful. Controlling sites where eggs accumulate is also very important.

## HORSE AND DEER FLIES

Horse flies (*Tabanus* spp.) and deer flies (*Chrysops* spp.) can give painful bites to horses. They are also most active during the summer and feed during the day. Their bites create painful pruritic papules and wheals that can progress into chronic nodular ulcerated, crusted lesions. Lesions are usually found on the lower legs but can be found anywhere on the body. Unlike many of the other insect hypersensitivities, lesions are usually focal rather than diffuse. Lesions can become very proliferative and mimic other nodular ulcerative lesions, such as those caused by *Habronema* spp., *Pythium* spp., and squamous cell carcinoma. Biopsies are indicated if any question about the diagnosis exists. Treatment is similar to that for *Culicoides* hypersensitivity.

## MOSQUITOES

Mosquito-bite hypersensitivity can create papular and urticarial eruptions, usually on the lateral aspect of the body. The major species affecting horses are *Aedes* spp., *Anopheles* spp., and *Culex* spp. They are most active at dusk and directly after sunset. Water is required for breeding and is an important area to target for treatment and control. As with *Culicoides* hypersensitivity, a few horses may show signs of airway disease concurrent with skin disease, possibly due to aerosolized insect allergens. In some horses with collagenolytic granulomas and eosinophilic folliculitis, clinical signs may be induced by a hypersensitivity to mosquito bites. Diagnosis and treatment are similar to the other insect hypersensitivities. Drainage and control of standing water is particularly helpful for mosquito control.

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## CHAPTER 4.5

# Mites and Ticks

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### MANGE (MITE INFESTATION)

Mites that cause mange usually are responsible for highly contagious diseases (Table 4.5-1). Because the entire life cycle occurs on the host, they are permanent parasites. The degree of host specificity varies. The multiplication of the mite on the host is theoretically exponential until the nonspecific and specific immune reactions of the host limit the number of mites. It is important to remember that these infestations may produce typical signs in some animals whereas others may exhibit few clinical signs or may be asymptomatic carriers, at least initially.

#### Psoroptic Acariasis

Mites of the genus *Psoroptes* infect ungulates and rabbits. Although the exact identification of these species remains controversial, horses have been said to be sensitive to *Psoroptes equi*. Other mites in this genus are *Psoroptes cuniculi* (rabbits), *Psoroptes natalensis* (cattle), and the most common species—*Psoroptes ovis* (sheep and cattle worldwide). Psoroptic mites do not burrow, and the life length of the entire cycle greatly varies from 9 to 90 days.

Infestation in horses by *Psoroptes* spp. is uncommon in most countries. *P. equi* infestation is highly contagious and host-specific in horses. The parasites are responsible for “mane and tail mange,” or otoacariasis. Horses with long, thick, and unclean coats may be more susceptible. Classic initial lesions are found at the base of the mane, the forelimbs, and the base of the tail. The lesions may then slowly extend over the body. Pruritus is generally intense and results in broken hairs. Papules and vesicles appear and serum collects to form crusts in the hairs. The scabs are usually moister than in sarcoptic infection. On the dorsum from the base of the neck to the tail, blood red lesions that easily bleed when brushed may develop.

*Psoroptes* mites, probably *P. cuniculi*, have also been reported to cause irritation, head shaking, rubbing, and drooping ears.

#### Sarcoptic Acariasis

Sarcoptic mange due to *Sarcoptes scabiei equi* was a major problem in groups of horses during the nineteenth century. It now seems to be a rare or even eradicated disease in most of Western Europe and North America. However, the distribution of the parasite is unknown in many countries, and the disease may reappear anywhere due to the frequent shipping and movement of horses. The different stages of *Sarcoptes* organisms, especially females, burrow

in the horny layer of the skin, and the development cycle from egg to ovigerous female is about 12 days.

Sarcoptic acariasis is characterized by a generalized intensely pruritic and highly contagious dermatosis. Classic descriptions of this disease mention initial lesions mainly on the head and neck, where multiple papules and a “moth-eaten” alopecia develop. These initial lesions are followed by a rapid caudal and ventral spread, and in chronically affected horses, the lesions become generalized. The most striking lesions are multiple nonfollicular papules that are covered by small crusts, which correspond to the location of burrowing mites. With chronic infestation the skin develops alopecia and becomes grayish, thickened, and wrinkled. Complications of self-trauma or super-infections may occur. Although typical equine sarcoptic mange seems to have become extremely rare, occasional cases have been described in Northern Europe with different characteristics, such as the absence of apparent intraspecies transmission and a different presentation with multifocal plaquelike lesions. It has been suggested that such cases could be due to a nonspecific variety of *Sarcoptes* organisms, perhaps of red fox (*Vulpes vulpes*) origin.

#### Chorioptic Acariasis

*Chorioptes* mites live on the surface of the skin, do not penetrate the epidermis, and do not bite like *Psoroptes* varieties. The infection is generally less severe and less pruritic than sarcoptic or psoroptic acariasis. The disease, also called *foot (or leg) mange*, remains a common but probably underdiagnosed or misdiagnosed disease in many countries. It is relatively common in Western Europe and is caused by *Chorioptes equi* or *Chorioptes bovis*. The disease is more severe in winter and may seem to resolve in summer. It is considered to be more frequent in draft breeds with long hairs (“feathers”) on the feet. The lesions are usually on the fetlock and pasterns and consist of slight erythema, papules, and crusts. Hind legs are always initially and more severely affected. The suggestive lesions remain generally localized to the lower limb, but the author has observed cases of extension onto the entire leg and the ventrum (white line, ventral midline dermatosis), which was only characterized by a discrete scaling. Tail involvement also has been described. Pruritus causes the horse to stamp and bite and is sometimes perceived by the owner during the night. Secondary self-trauma and infected pododermatitis occur in chronic cases. For this reason Chorioptic mange is in the differential of most cases

Table 4.5-1  
Common Mites, Ticks, and Ectoparasites in Horses

Group	Parasite	Disease	Comments
Astigmata	<i>Sarcoptes scabiei equi</i>	Sarcoptic acariosis	Rare in most North American and European countries
	<i>Chorioptes equi</i>	Sarcoptic mange Chorioptic acariosis Chorioptic mange	Common/underdiagnosed
	<i>Psoroptes equi</i> , <i>Psoroptes ovis</i>	Psoroptic acariosis Mane and tail mange	Rare
Prostigmata	<i>Psoroptes cuniculi</i>	Psoroptic otoacariosis	Rare
	<i>Demodex equi</i>	Demodicosis	Occasionally seen; more common in ponies?
	<i>Demodex caballi</i>		
	<i>Neotrombicula</i> ( <i>Trombicula autumnalis</i> )	Harvest (bug) Trombiculidosis Dermatitis, head shaking	Very common in Europe
	<i>Eutrombicula alfreddugèsi</i>	Chiggers Trombiculidosis	Americas
	<i>Eutrombicula sarcina</i>	Scrub itch mites Trombiculidosis	Asia, Australia
	<i>Pyemotes tritici</i> ( <i>Pyemotes ventricosus</i> )	Straw itch mite Dermatitis	Rare; Americas, other countries
Gamasida Ixodida	<i>Cheyletus</i> spp.	Dermatitis	Rare; worldwide
	<i>Dermanyssus gallinae</i>	Dermatitis	Rare; worldwide
	<i>Ixodes ricinus</i>	Dermatitis	Hard ticks in Europe
	<i>Dermacentor reticulatus</i>		
	<i>Dermacentor marginatus</i>		
	<i>Rhipicephalus bursa</i>		
	<i>Hyalomma</i> spp.		
	<i>Ixodes</i> spp.	Dermatitis	Hard ticks in America
	<i>Dermacentor variabilis</i>		
	<i>Dermacentor</i> ( <i>Anocentor</i> ) <i>nitens</i>	Otitis, dermatitis	United States (Florida, Texas)
	<i>Hyalomma</i> spp.	Dermatitis	Hard ticks in Africa, Asia, and Australia
	<i>Amblyomma</i> spp.		
	<i>Rhipicephalus</i> spp.		
	<i>Boophilus</i> spp.		
	<i>Margaropus winthemi</i>		South Africa Winter horse tick
	<i>Otobius megnini</i>	Spinose ear tick Otitis	Soft ticks: Americas, India, South Africa
	<i>Ornithodoros sensu lato</i>	Dermatitis	Mainly Africa

of pododermatitis (pastern dermatitis, scratches, grease heel) in horses.

### Trombiculidosis

Trombiculids of various species (*Trombicula* or *Neotrombicula*; see Table 4.5-1), also called *chiggers* or *harvest mites*, are commonly found in horses. Only the larvae (not the nymphs or the adults) are parasitic. These larvae have a more or less seasonal activity (fall in the Northern Hemisphere). Although the parasitic phase of one individual larva is relatively short (several days), the clinical signs last several weeks due to the acquisition of new larvae in the environment and the persistent irritation from stylostome secretions by the larvae in the skin. Trombiculids are found in grass and hay and prefer the feathers of the

fetlock but also the mane, the tail, and the face (periocular, lips, and periocular). The mites also can be found on the legs and abdomen. Trombiculids generally accumulate in small orange clusters. The parasitism is often asymptomatic. In some horses, lesions—such as papules; urticarial wheals; tufts of erect hairs and crusts; or erythema with exudates, usually on the fetlocks—occur and are accompanied by variable pruritus. *Trombicula autumnalis* has also been responsible for head shaking in horses. Secondary infections may occur, particularly on the fetlocks.

### Demodicosis

Demodicosis is a rare disease in horses, and few clinical descriptions are available. *Demodex* species are host-specific and transmitted very early in life. The infection is not

contagious, and *Demodex* mites may be found in normal skin. In case of demodicosis, lesions generally develop on the head, neck, withers, and hindquarters. The proliferation of parasites produces a diffuse or patchy alopecia or thin coat as well as dry and scaly skin with occasional papules and pustules. The condition is not pruritic.

Two morphologically different *Demodex* species are isolated from horses. *Demodex caballi* is the longer of the two species; it is found in the meibomian glands and on the muzzle and is generally considered nonpathogenic. *D. equi* is the shorter species and has a more generalized body area distribution. The causes for equine demodicosis are unknown, and no treatments have been validated.

### Dermanyssus Dermatitis

*Dermanyssus gallinae* is a common blood-sucking mite (parasitiform) that usually feeds on poultry. These mites are nocturnal and during the day hide in crevices and cracks, where they reproduce. The life cycle can be completed very rapidly (7 days), and fed adults may survive for months without feeding again. Infestation of horses was common when horses were housed close to poultry. The signs are mainly a nocturnal pruritus associated with papules, erythema, and crusts on feet and legs.

### Nonparasitic Mites

Episodes of dermatitis in horses can be due to nonparasitic mites. The straw itch mite, *Pyemotes tritici* (*Pyemotes ventricosus* or *Pediculoides ventricosus*) parasitizes larvae of grain-destroying insects. Occasionally they can pass from grains, straw, or hay (alfalfa) onto man or animals, thus causing a more or less severe dermatitis. Pseudocontagious episodes of papular and vesicular dermatitis have been described in horses and humans. In horses, lesions most often develop on the neck and head and consist of alopecia with multiple papules. Observations of *Pyemotes tritici* in horses has been mainly in the United States, but the mite is recognized in many parts of the world.

Other mites (sarcoptiforms or trombidiforms) may proliferate in hay during storage. They may cause a mechanical irritant dermatitis. The author has observed such cases on the face and neck of horses due to *Cheyletus eruditus*, a cheyletid predator of other mites with a worldwide distribution.

These nonparasitic mite infestations may be confused with chigger infestations that occur during the same period (May to October in the Northern Hemisphere).

### TICKS

Horses are exposed to a number of species of ticks, according to the geographic area (see Table 4.5-1). The importance of ixodid ("hard") ticks is mainly due to the transmission of infectious diseases like babesiosis or ehrlichiosis. However, a direct effect can be observed due to the skin damage, mechanical irritation, and pain (ticks preferentially bite areas where the skin is thin) or secretion of neurotoxic products. Ticks are also important in horses because they favor the development of bacterial infections (such as dermatophilosis) or myiasis.

Tick bites from adult ticks occur more commonly at the base of the ears, the anal and genital area, skin folds, and fetlocks and are characterized by erythema, papules, and black crusts. When larval forms are involved, they are generally numerous and may produce a papular dermatitis with tufts of erect hairs and papules. The entire body can be affected, particularly the head and limbs. One unique condition has been described in horses in Australia and is caused by immature stages of *Boophilus microplus* that results in an intense pruritus of sudden onset. The lesions, mostly localized to the head and limbs, are multiple papules and wheals that surround feeding larva and are probably due to a hypersensitivity response.

### Ear Infestations

The spinose ear tick *Otobius megnini* (an argasid, or "soft" tick) originated in western North America and has spread to Africa and Asia. It is primarily a parasite of horses, donkeys, and cattle but has been recorded from a range of hosts. The larvae infest the host and develop in the ear canal in two successive nymphal stages. The parasitic phase may last from 5 weeks to several months. *Dermacentor (Anocentor) nitens*, also called the tropical horse tick, lives deep in the ear canal. This is a one-host tick (larva to adult on the same host). The ear ticks cause intense inflammation and irritation. The lesions vary from benign otitis with periaural alopecia to thick crusts and abundant cerumen with pruritus or even ataxia with neurologic signs.

Remembering that other parasites besides ticks may produce otitis in horses is important. *Psoroptes* spp. may cause a true otacariasis with erythema, excess cerumen, and head shaking comparable to psoroptic infestation in rabbits. Head shaking may be the only sign associated with a trombiculid infestation.

### DIAGNOSIS

Identification of mite infestation is initially based on clinical and epidemiologic observations. In cases of pruritus associated with mite infestation (*Psoroptes*, *Sarcoptes* mites) the itch reflex can be obtained in some horses. When scratched over the lateral neck or the withers, they tuck the nose close to the chest or extend the head and make a smacking noise with marked movements of the upper lips. Different mites may cause similar clinical signs, and the treatment may be the same. However, a precise diagnosis is recommended because their prognoses, contagion potential, and overall control can differ.

Acarial infestations can be contagious (mange mites) or pseudocontagious (trombiculids, ticks, and nonparasitic mites). Even apparently healthy horses can be infested.

In cases of mange infestation, a nonspecific eosinophilia is sometimes present. The histopathologic findings in such diseases are also usually nonspecific unless parasites (or fragments thereof) are present in the sections. If present, *Sarcoptes* spp., *Psoroptes* spp., the stylostome of trombiculids, and the chelicerae of ticks are most often seen. Skin biopsies reveal varying degrees of superficial perivascular dermatitis with numerous eosinophils that are compatible both with ectoparasites and hypersensitivities. Occasionally a deep



perivascular dermatitis with lymphoid nodules is observed. The presence of microabscesses with eosinophils is a suggestive finding for ectoparasites. However, in many cases secondary infections may change the histopathologic pattern, thus masking suggestive findings. One exception is demodicosis, in which biopsies may reveal hair follicles distended to varying degrees with recognizable demodectic mites.

A definitive diagnosis of mite or tick infestation is based on recovery of the organism from the affected host. Multiple skin scrapings are generally needed to recover superficial mites such as *Sarcoptes* or *Chorioptes*. Skin scrapings can be negative in asymptomatic carriers or in chronic disease. As in the dog, skin scrapings may reveal the mites, their eggs, or feces. It is preferable to clip the hair before sampling affected skin areas.

In cases of demodicosis (a deep or follicular mite) multiple skin scrapings may also be necessary. In one case in Minnesota only 9 of 42 skin scrapings were positive, thus giving a total of 12 mites. The skin should be grasped and squeezed between the thumb and forefinger to improve the evacuation of follicular content. Ticks are carefully collected with forceps to obtain the entire rostrum necessary for identification.

Identification of mange mites is relatively easy (they measure 0.25-0.75 mm in length). *Sarcoptes* mites have a rounded body with a short rostrum and short legs ending in long peduncles; *Chorioptes* mites have a conical rostrum and relatively long legs with suckers directly fixed to the extremity; and *Psoroptes* mites are larger with an elongated rostrum and long legs with triarticulate sucker-bearing peduncles. Trombiculids are characterized by their orange color (size 0.25 to 1 mm), the long and plumose setae, and a typical rostrum. Identification of adult hard ticks is relatively easy at the genus level, and *Otobius* nymphs have a typical spiny integument and a ventral rostrum. Precise identification of species and of larval stages of ticks is a matter for the specialist.

## CONTROL

The methods and efficacy of control of mites and ticks in horses depends on each parasite. Many acaricidal drugs can be safely used in horses with the exception of Amitraz. Topical acaricidals safely used in horses are organophosphates (i.e., dimpylate, malathion, coumaphos, phoxim), organochlorines (lindane), carbamates (carbaryl), and lime sulfur. Dosages are not detailed here. The drugs available or licensed for horses depend on the country. Other topical products such as phenylpyrazole (fipronil) are well-tolerated and have demonstrated successful off-label use against *Chorioptes* spp. Formulations such as sprays, sponge-ons, and powders are more effective against superficial and temporary parasites, whereas topical control of mange mites often requires clipping the hair coat and thorough application. The frequency of application is usually once or twice a week for at least 3 weeks. The systemic acaricidal most commonly used is ivermectin; the usual dose is 0.2 mg/kg every 2 weeks, given 3 times. However, the route of administration influences the efficacy of ivermectin. Orally

administered ivermectin produces a peak blood concentration 4 to 6 hours after administration, with a higher concentration than the injectable route until 36 hours after administration. At that time the concentration rapidly decreases, whereas the blood concentration of injectable ivermectin increases for four days and maintains high levels for ten days, thus probably making it more effective. However, it should be borne in mind that injectable ivermectin can cause serious side effects in some horses. In two studies with different protocols of oral ivermectin there was no complete cure in some of the treated horses. The best treatment for the control of mange is probably to combine the systemic action of macrocyclic lactones with the application of a topical acaricidal.

Frequent application of pyrethroids is probably the treatment of choice against ticks in situations of risk for transmission of tickborne diseases. Parasitocidal treatments must be also combined with other methods: isolation of all contaminated horses (for contagious infestations), avoidance of infested areas (important for chiggers, ticks, and *Dermanyssus* spp.), change of food source (*Pyemotes* and other hay or straw mites), and disinfection of barns and material (mange, *Dermanyssus* spp.). Medication for the control of inflammation and/or pruritus (i.e., corticosteroids) is generally contraindicated except in trombiculidosis.

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## CHAPTER 4.6

# Fly Control

LANE FOIL

CAROL FOIL

*Baton Rouge, Louisiana*

**F**lies (Diptera) are ubiquitous pests of horses. The general life cycle of flies includes four stages: egg, larva, pupa, and adult. Flies that depend most on domestic animals for energy sources are the easiest to control. In some species of flies, the adults use domestic mammals as a primary energy source (e.g., horn flies). However, in many free-living *Diptera* species, only the adult female feeds on vertebrates, and a single blood meal is needed as a source of energy for egg production. These pests are the most difficult to control. Box 4.6-1 provides management strategies for common equine-biting flies.

Boxes 4.6-2, 4.6-3, and 4.6-4 provide insecticidal and repellent compounds currently available in formulated pesticides for use on or around horses. Because the majority of pesticides for horses are available for over-the-counter sales to horse owners, this chapter will focus on integrated management strategies so that veterinarians can best advise horse owners on controlling these ectoparasites.

### TABANIDS, BLACK FLIES, AND BITING MIDGES

Tabanids, black flies, and biting midges are not livestock-dependent, and it is impossible to control the larval habitat.

#### Tabanids

In North America, tabanids are horse flies (*Tabanus* spp.) and deer flies (*Chrysops* spp.), which are 6- to 11-mm, yellow-orange flies with dark body markings and mostly with patterned wings. The term *horse fly* describes a large, diverse group of flies that vary in color, body markings, wing markings, and size (9-33 mm). The females take blood meals infrequently only to support egg development. They are active from dawn through dusk. The larvae are predators of invertebrates in a variety of aquatic to semiaquatic habitats and take from 3 months to 2 years to develop. Tabanids serve as mechanical vectors for more than 35 pathogenic agents of livestock including equine infectious anemia virus, and *Microsporum gypseum* dermatophytosis. They are painful biters and cause extreme annoyance and blood loss; local reactions to bites include dermal nodules. Protection from adult female tabanids is the only management for this group. The frequent use of pyrethroid-based insecticide/repellent is the only practi-

cal means of protecting horses. Pastures located away from wooded areas are preferable. Few tabanid species enter barns; thus stabling of animals during peak tabanid activity can help. An electrified insect light trap hung inside barns can be useful when tabanid species are present, but these traps are not useful outside.

#### Black Flies

Black flies (*Simulium* spp.) are small (2-5 mm), diurnal pests of horses and man. These flies are best recognized by their "humpbacked" appearance. Females blood-feed every 3 to 5 days; the larvae develop in moving water; and mass emergence of flies can occur from one to several times per year, with an outbreak lasting 2 weeks to 3 months. Population density normally reduces with distance from the larval habitat, but swarms that migrate on winds can travel several hundred miles. Flies that feed inside the ears and on the head, neck, chest, medial thighs, and abdomen can cause extreme annoyance and pruritus. Massive numbers can even cause death by release of a toxin in the flies' saliva. Hypersensitivity can also occur. The horse's ears are the best place to look for these pests; the individual bites cause pinpoint hemorrhage and bloody crusts, and they have been implicated in transmission of the papillomavirus that causes aural plaque in horses. Protection from adult flies is the only management strategy available. Stabling of horses during peak fly activity periods can be helpful because black flies normally do not enter buildings even through open windows. Ear nets and/or frequent treatments with repellents can provide individual protection of horses. Application of petroleum jelly inside the ears after clipping can also help. Massive outbreaks are often managed by local government agencies.

#### Biting Midges

Biting midges are small flies (0.6-5.0 mm) and are commonly referred to as "punkies," "no-see-ums," or "sand flies." Two genera, *Culicoides* and *Leptoconops* (valley black gnat), are the major pests of horses in the United States. Females take blood meals at 3- to 4-day intervals. *Leptoconops* spp. larvae develop in sandy or clay-silt soils and emerge as adults following rainy seasons. *Culicoides* spp. larvae develop in a variety of habitats, including water, decaying vegetation, or manure. In some species, multiple generations can be produced yearly. These flies are most active in calm wind conditions during crepuscular and nocturnal periods. They have an extremely irritating bite

**BOX 4.6-1****Management Strategies for Common Equine Biting Flies****Stabling**

Tabanids—diurnal and crepuscular periods  
 Black flies—diurnal and crepuscular periods  
 Biting midges—under fans; nocturnal and crepuscular periods; insecticide-treated screens

**Exclusion Devices**

Black flies—ear nets  
 Culicoides—fly blankets  
 House flies—face masks  
 Face flies—face masks

**Hay and Manure Management**

Stable flies—in particular, hay in pastures  
 House flies—general sanitation

**Cattle Management**

Horn flies—control pest on natural host  
 Face flies—undisturbed cattle manure requisite for larval development

**Water Management**

Mosquitoes—only certain species  
 Biting midges—only certain species

**Restricted Grazing or Movement**

Tabanids—allow escape from wooded areas  
 Culicoides—open breezy pastures

**Premise Insecticide Application**

Mosquitoes  
 Stable fly  
 House fly

**Fly Strips or Traps**

House flies

**Frequent Application of UV-Light Stabilized Repellents/Insecticides**

Black flies  
 Culicoides  
 Face flies  
 Horn flies  
 House flies  
 Mosquitoes  
 Stable flies  
 Tabanids

**BOX 4.6-2****Pesticides Recommended for Fly Control on Horses****Residual Insecticides****Pyrethroids**

Cypermethrin  
 Permethrin  
 Resmethrin

**Organophosphate feed-through**

Tetrachlorovinphos

**Phenylpyroazole**

Fipronil\*

**Other Compounds****Repellants**

Dipropyl isocinchomeronate (MGK 326)  
 Butoxypolypropylene glycol (Stabilene)  
 N,N-diethyl-m-toluamide (DEET)

**Botanicals**

Pyrethrins (repellent and insecticidal)  
 Citronella (repellent)  
 Simmonosia-Chinensis (repellent)

**Synergists**

Piperonyl butoxide  
 N-octyl bicycloheptene dicarboximide (MGK 264)

\*Not approved, but useful.

Categories may overlap; for example, pyrethrins are also insecticidal, and pyrethroids are repellent. Note that many of the most effective products use these ingredients—especially pyrethroids, repellents and synergists—in combination. Also, stabilization of the ingredients with sunscreens for horses on pasture and silicates for binding ingredients to the hair for sweat protection is useful. Types of product applications are listed in Box 4.6-4.

## BOX 4.6-3

**Premise Treatments****Sprays, Powders, and Fogging Compounds**

Carbaryl dust  
 Chlorpyrifos  
 Cyfluthrin  
 Cypermethrin  
 D-Trans allethrin  
 Deltamethrin  
 DDVP strips  
 Diazanone  
 Esbiothrin  
 Malathion  
 Methomyl fly bait  
 Mucalvre fly bait  
 Naled  
 Nithiazine strips  
 Permethrin  
 Resmethrin  
 Tetramethrin  
 Synergized pyrethrins

## BOX 4.6-4

**Forms of Repellents and Insecticides for Horses\***

Sprays  
 Stabilized sprays  
 Face lotions  
 Roll-ons for face and head  
 Wound treatment gels and ointments  
 Clothing sprays  
 Fly collars, leg bands  
 Wipe-ons and towelettes

\*The most useful are stabilized with sunscreens, and some are further stabilized by formulation in silicon-containing products. Method of application is often a critical variable. For example, wipe-on products can be more effective than other methods for application of the same chemical product.

and thus are important causes of horse worry and pruritus when numbers are high. *Onchocerca cervicalis* is transmitted by *Culicoides* spp. *Culicoides* organisms are being investigated as potential vectors for West Nile viral encephalitis and are important vectors for other viral infections of horses in other parts of the world (e.g., African horse sickness). Some species can induce a seasonal familial hypersensitivity syndrome, *Culicoides* hypersensitivity. Pruritus is often most intense along the base of the mane and tail and over the withers; however, the chest, ventral, and facial areas can be affected. Onset of pruritus correlated with *Culicoides* spp. feeding periods aids in diagnosis, although many horse owners remain rel-

atively unaware that these tiny insects are visiting their horses.

Hypersensitive horses can be treated with corticosteroids, but long-term management of the allergy is based upon protection from adult gnats. Stabling of horses during peak feeding times is advisable to make protection from the flies easier to achieve. Because of the weak flight capabilities of *Culicoides* organisms, fans—even in open-sided stalls—can provide protection under some conditions. Screened windows impregnated or routinely treated with residual repellent insecticides such as permethrin can also afford protection. Frequent application of repellents should also be recommended. Relatively open and airy pastures are preferable to low-lying fields surrounded by woodlands. In moderate climates, fly-protecting blankets may be useful during times when the flies are active. Water management recommended for mosquito control may also aid in reducing endemic populations of some gnat species. A study in France recently showed that application of permethrin-based sprays every two weeks could be sufficient to allow improvement of clinical signs in some horses with *Culicoides* hypersensitivity.

**STABLE FLIES, HORN FLIES, AND MOSQUITOES**

Stable flies, horn flies, and mosquitoes are dependent on mammals for energy and control of their larval habitats can be useful.

**Stable Flies**

The adult stable fly, *Stomoxys calcitrans*, superficially resembles the house fly but can be distinguished easily by the prominent blood-sucking mouthparts which extend anteriorly. The optimal stable fly larval habitat is hay, silage, or grass clippings contaminated with urine, water, and manure. Multiple generations are produced per year. Both sexes are blood-feeders and feed primarily on the legs and abdomens of horses. Blood loss and annoyance as well as wheals, crust, cutaneous papules, and nodules have also been associated with stable fly feeding. The stable fly is capable of mechanically transmitting pathogenic agents, including equine infectious anemia virus, dermatophilosis, and dermatophytosis. Both stable flies and house flies are considered vectors of habronemiasis. Repellents and residual insecticides can be useful in stable fly control, and materials should be directed primarily at the legs. Premise sprays are also recommended, and it should be noted that flies often choose a sunny wall as a resting spot before and after taking a blood meal. However, larval habitat management is the most important consideration in stable fly control. Also, feed-through fly control medications may also be useful if the majority of the animals on the premise are treated. The use of elevated hay feeders and otherwise proper hay disposal can prevent problems for pastured animals.

**Horn Flies**

Horn flies, *Haematobia irritans*, are small (4 mm) obligate ectoparasites of cattle; the entire adult life is essentially spent upon the host. Horn fly larvae develop in fresh bovine ma-

nure; multiple generations are produced per year. Horses are attacked and worried by horn flies (both sexes are blood-feeders) when they are pastured with or near cattle. Horn flies feed in aggregates (head-downward), primarily upon the shoulders, neck, withers, and abdomen, and may contribute significantly to the commonly observed seasonal ventral midline dermatitis of horses. Because this pest depends on cattle manure to complete the life cycle and spends the majority of its life on the host, the horn fly is relatively easy to control on horses. The use of residual insecticide sprays on horses at labeled intervals adequately controls horn flies. Obviously, separation from cattle or control of the flies associated with the cattle can reduce the problem.

## Mosquitoes

Female mosquitoes blood-feed every 3 to 4 days. The most active feeding period of most species is the first 2 hours following sunset. Larvae develop in permanent water sources or in habitats prone to water level fluctuation, including pastures, tree holes, and artificial containers. Multiple generations are produced yearly, and the life cycle can be completed within a week during warm weather. Explosive populations of mosquitoes can create considerable annoyance for horses. However, the primary impact of mosquitoes on equine populations is the transmission of viruses; in particular, Western (WEE), Eastern (EEE), Venezuelan (VEE), and West Nile equine encephalitis. However, routine vaccination, rather than mosquito control, is needed for protection against the encephalitides.

Mosquito larval habitat control is frequently beneficial when these habitats are found on the premises. Larval chemical control agents can be in the form of insecticides, surfactants, or biologic control agents, although professional consultation is warranted to avoid harming nontarget species of insects. Local government mosquito abatement agencies usually can be contacted about mosquito control off-premises. On premises, drainage of standing water, frequent drainage of troughs, cleaning of rain gutters, and elimination of man-made water containers can greatly reduce mosquito problems. Minnows (e.g., *Gambusia* organisms) can help in water sources that cannot be drained. The use of timed overhead sprayers, foggers, and/or treatment of resting sites (walls) and horses with residual insecticides can help to keep mosquito populations at a moderate level. Frequent applications of repellents during peak mosquito outbreaks are often required but are often inadequate in massive emergence episodes.

## HOUSE FLIES AND FACE FLIES

House flies and face flies depend on manure to reproduce. The house fly (*Musca domestica*) and face fly (*Musca autumnalis*) can be differentiated by the color of the lateral aspects of the adult abdomen (yellowish—house fly, black—female face fly, and orange—male face fly). The face fly larva is yellowish, and the pupa is dirty-white, whereas the house fly larva is white, and the pupa is reddish-brown. Face fly larvae mature only in undisturbed cattle manure. House fly larvae develop best in manure but mature in a wide variety of organic debris. Both species can produce multiple generations per year. Because they feed on lac-

rimal secretions or on wounds, the face fly and house fly can cause considerable worry to horses. House flies and stable flies are vectors of habronemiasis. The house fly has also been incriminated in the transmission of over 60 vertebrate pathogens. In addition, large numbers of house flies on an equine facility can cause problematic interactions with non-horse owning neighbors. The face fly has been shown to transmit eye worms of the *Thelazia* spp.

For the house fly, larval habitat control is considered of primary importance. Proper disposal of hay, bedding, and manure should be part of any fly control program. Because face fly reproduction requires undisturbed cattle manure, treatment of proximal cattle with insecticidal ear tags can be beneficial. In multiple horse facilities, the use of feed-through fly-control drugs or commercially available parasitoids may be useful, but neither substitutes for proper management of manure. Proper composting is the most effective house fly-management tool when attention is paid to the achieving sterilizing temperatures in the compost structure. For individual horses, residual insecticide/repellent application on the face and neck can aid in house fly and face fly control. Commercially available “fly masks” or face masks attached to halters can also reduce eye feeding by flies. Combinations of premise sprays, residual wall or timed-space spray-pyrethrin systems are helpful; in addition, baits, sticky traps, or electric grids are often used for adult house fly control.

## MYIASIS

Myiasis is the infestation of tissue by fly larvae. Facultative myiasis can be produced by a variety of fly larvae—notably *Cochliomyia macellaria* (secondary screwworm), *Phormia regina* (black blow fly), and *Phaenicia* spp. (green or bronze blow flies)—that routinely develop in carrion and other places. The larvae can develop in necrotizing skin lesions of horses. Maggot-infested wounds should be thoroughly cleansed and debrided. Treatment with insecticide-containing wound ointments, in addition to supportive treatment, is recommended. Prevention by treatment of wounds with repellents is helpful.

*Hypoderma lineatum* and *Hypoderma bovis* (cattle grubs) are obligate parasites of cattle that can occasionally infest horses. Subcutaneous and dermal nodules are found most frequently in the spring and early summer and are most often located dorsally. A characteristic central breathing pore may be found in most lesions. Individual lesions may be resolved surgically, but ivermectin at standard dosages has been reported to control development of *Hypoderma* spp. larvae. Migration of *Hypoderma* larvae can also produce intracranial equine myiasis; clinical signs vary relative to the location and magnitude of larval migration.

## HORSE BOTS

*Gasterophilus* spp. are flies that as adults are superficially bee-like in appearance. The life cycle of bot flies takes about one year. Eggs are firmly attached to the hairs of horses and larvae (bots) live inside the horse's mouth for a few weeks and burrow in the mucous membranes of the lips and tongue, thus causing transient irritation. The larvae then migrate to the stomach, grow for up to 10 months until be-

ing passed in the manure, and pupate in the ground for 1 to 2 months. Asynchronous development and discharge of larvae that result in extended periods of oviposition occurs. Stomach bots can cause mechanical blockage, colic, or rupture of the stomach wall and resultant peritonitis. Many of the treatments for internal parasites effectively control stomach bots when routinely administered.

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## CHAPTER 4.7

# Cutaneous Habronemiasis

CHRISTINE A. REES  
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 College Station, Texas

Cutaneous habronemiasis ("summer sores") is a common cause of nodular and ulcerative skin disease in horses. The ulcerative and proliferative skin lesions of this condition cause discomfort for the horse and are cosmetically displeasing to the horse owner. Clinical signs associated with cutaneous habronemiasis include pruritus, chemosis, blepharospasms, epiphora, and dysuria.

Ivermectin was originally released from the manufacture in the 1980s and has been shown to be 99.9% effective in killing *Habronema* spp. The high efficacy may lead some veterinarians to conclude that a horse treated with ivermectin will not develop cutaneous habronemiasis; however, this condition is often diagnosed in a horse with a history of ivermectin use.

So why is cutaneous habronemiasis still a problem? To better understand this problem, a review of the history, clinical signs, diagnostic approach, and treatment options for cutaneous habronemiasis is provided.

### ETIOLOGY AND PATHOGENESIS

Cutaneous habronemiasis is seasonal nodular skin condition in horses caused by a hypersensitivity reaction to stomach worm larvae in the skin. Three species of equine stomach worms may be involved: *Habronema muscae*, *Habronema majus* (*Habronema microstoma*), and *Draschia megastoma* (*Habronema megastoma*). In the normal life cycle, the flies deposit infective *Habronema* or *Draschia* larvae near the horse's mouth; the larvae are swallowed and then develop to adults within the stomach. Eggs are shed in the feces, ingested by flies, and then develop to the infectious

stage. Cutaneous habronemiasis results when the larvae are deposited by the fly into open wounds or chronically moist areas on the horse's skin, such as the commissure of the mouth or frictional surfaces affected by excessive sweating. The larvae penetrate the dermis to cause inflammation and/or a hypersensitivity reaction, thus resulting in pruritus and the development of skin lesions.

Support for this idea of a hypersensitivity (allergic) reaction comes from the fact that recurrence of cutaneous habronemiasis has been reported from year to year in the same horses and that this condition is a seasonal problem. In addition, a few horses have been treated and cured when only systemic glucocorticoids were administered.

### CLINICAL SIGNS

Cutaneous habronemiasis is most commonly seen during the warm months of the year (spring and summer). One or more horses may be affected in a herd. Some horses may develop these lesions annually. Cutaneous lesions commonly develop in areas of previous trauma.

The lesions associated with cutaneous habronemiasis consist of ulcerated, single or multiple nodular growths on the legs, prepuce, urethral process of the penis, and medial canthus of the eye. One or more of these locations may be involved in a particular horse. Other areas of the body that have been previously traumatized may also be affected. Regardless of the type or location of the skin lesions, pruritus is consistently present and varies from mild to severe.

Ocular lesions other than the skin of the medial canthus include the conjunctival sac, the lacrimal duct, and

ing passed in the manure, and pupate in the ground for 1 to 2 months. Asynchronous development and discharge of larvae that result in extended periods of oviposition occurs. Stomach bots can cause mechanical blockage, colic, or rupture of the stomach wall and resultant peritonitis. Many of the treatments for internal parasites effectively control stomach bots when routinely administered.

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Ocular lesions other than the skin of the medial canthus include the conjunctival sac, the lacrimal duct, and

the third eyelid. Yellow caseous material may be present in the eyes. This material consists of necrotic tissue, which encases the infective larvae, and it may be plaque-like in appearance. Severe ocular problems may result, including epiphora, chemosis, and photophobia.

Lesions on the urethral process cause additional problems for the affected horse. If the cutaneous lesions are large enough and complete or partial obstruction of the urethral opening occurs, dysuria may result. Pulmonary habronemiasis has been reported but is rare.

## DIAGNOSIS

The differential diagnoses for cutaneous habronemiasis include squamous cell carcinoma, pythiosis, infectious granulomas (bacterial, fungal), exuberant granulation tissue ("proud flesh"), and equine sarcoid.

The history and physical examination findings may strongly suggest the diagnosis of cutaneous habronemiasis. However, the most useful diagnostic test is a skin biopsy. One of the problems with the skin biopsy is that intralesional larvae are not always present. The largest possible biopsy sample from deep within the affected tissue or multiple samples (minimum of 3, at least 6 mm in diameter) will maximize the pathologist's chances of finding the larvae and making a definitive diagnosis.

Histologically, the reaction seen with cutaneous habronemiasis is an eosinophilic granulomatous reaction with collagenolysis, some mast cell infiltrate, and epithelioid macrophages or giant cells scattered throughout the collagenous lesion. Larvae in cross section are most commonly seen in areas of coagulation necrosis. In some cases the larvae are difficult to find histologically, and the history, physical examination findings, and presence of an intensely eosinophilic granuloma formation support but do not confirm the diagnosis of cutaneous habronemiasis. Regardless of whether the larvae can be found histologically, performing biopsies is very important because it helps the clinician definitively rule out several differentials such as neoplasia, foreign body granulomas, phycomycosis and ocular onchocerciasis.

In some cases the larvae may be seen cytologically from deep scrapings of the skin or from the exudate. The larvae are usually motile, large (3-mm  $\times$  60- $\mu$ ) larvae with a spinous process on the tail.

## TREATMENT

### Antiinflammatory Drugs

Because a hypersensitivity reaction to the larvae is believed to be one of the major causes in the pathogenesis of this skin disease, treatment usually involves some form of either topical or systemic steroid therapy. The most common steroids used in topical preparation are dexamethasone and triamcinolone. These steroids are most commonly combined with other medications such as dimethyl sulfoxide (DMSO), fenthion, and/or nitrofurazone. Oral steroids have also been used to minimize or control the hypersensitivity reaction. The usual antiinflammatory steroid dose used to treat cutaneous habronemiasis is prednisolone (1 mg/kg q24h) for 10 to 14 days and then tapered off over

a 2-week period. If this mode of therapy is advocated then the owners need to be warned of possible side effects such as laminitis and enterocolitis that are associated with steroid use in horses.

### Eliminating Parasites from the Skin

Systemic parasiticide treatment is used to eliminate the parasite from the skin. The most commonly used parasiticide is ivermectin, which is almost 100% effective in killing *Habronema* larvae. However, the half-life for orally administered ivermectin in horses is 66.3, plus or minus 4.7 hours; thus it is almost completely eliminated from the body in five half-lives or approximately 14 days. The manufacturer recommends that horses be treated with ivermectin every 2 months for control of internal parasites such as *Habronema* varieties. However, one study demonstrated that such a frequency of drug administration might not always be adequate in controlling *Habronema* spp. In this report, 5 of 31 horses required additional intramuscular treatment within 2 to 4 weeks with ivermectin to clear the *Habronema* infection. Parenterally administered ivermectin has a longer half-life than orally administered ivermectin (88.2,  $\pm$  9.1 hours for subcutaneous injection, versus 66.3  $\pm$ , 4.7 hours for oral administration). Therefore in cases of recurring cutaneous habronemiasis, ivermectin may need to be given more frequently than every 2 months.

A newer parasiticide agent, moxidectin, has a similar efficacy against *Habronema* organisms as ivermectin and may be considered for some of the more difficult cases of cutaneous habronemiasis. The recommended dose for moxidectin is 0.4 mg/kg orally. The half-life of this orally administered drug is similar to ivermectin, but, unlike ivermectin, the parent compound has been detected in the plasma for extended periods of time (ivermectin—30 days, whereas moxidectin—75 days) after treatment. This longer retention time provides a longer anthelmintic effect, which may be advantageous for treating difficult cases of habronemiasis.

Fly control with various sprays is usually recommended to prevent recontamination of the lesion with larvae. Because of longer residual activity, an oil-based fly spray is preferred over the water-based fly sprays.

Surgery is another method of eliminating the parasite from the skin. Surgical excision is especially useful in the treatment of large proliferative cutaneous habronemiasis lesions that have not reduced in size when the horse has been treated with systemic steroids. Surgery can also be used to debulk a lesion. For example, when proliferative lesions that involve the prepuce or urethral opening cause dysuria, routine surgical methods, cryosurgery, or lasers may remove the affected tissue. Success has been reported with each of these methods.

Topical or systemic parasiticides used to eliminate *Habronema* larvae from the skin include fenthion, trichlorfon, thiabendazole, ronnel, echothiophate (phospholine iodide) ophthalmologic drops, and ivermectin. These ingredients are used either by themselves or in combination with other ingredients.

The author has had the best results when topical and systemic treatments, which contain antiinflammatory



agents and/or antiparasiticide agents, have been used in combination. Fly control is essential to maximize the chances for success in treating and preventing recurrence of cutaneous habronemiasis in horses.

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## CHAPTER 4.8

# Folliculitis: Staphylococcal Pyoderma, Dermatophilosis, and Dermatophytosis

CATHERINE ANNE OUTERBRIDGE  
PETER J. IHRKE  
*Davis, California*

**F**olliculitis is a common skin disease in the horse. It can be caused by a number of etiologies—including infections with bacteria (*Staphylococcus*, *Streptococcus* or *Dermatophilus*), fungi (dermatophytes), and parasites (*Demodex*), or by autoimmune diseases (pemphigus foliaceus). Folliculitis is an inflammation of the hair follicle with accumulation of inflammatory cells within the lumen of the follicle. If the inflammation results in degeneration of the follicular wall with associated inflammation beyond the confines of the follicle and into the surrounding dermis and subcutis, the lesion is referred to as *furunculosis*.

Clinical signs of folliculitis include papules, serum exudation, crusts, alopecia, and easily epilated hairs. Nodular lesions and draining tracts are lesions that suggest furunculosis. Instances of infectious folliculitides due to staphylococcal pyoderma, dermatophilosis, and dermatophytosis are the most common in the horse.

### STAPHYLOCOCCAL BACTERIAL FOLLICULITIS

Bacterial folliculitis due to gram-positive staphylococcal species is seen worldwide. Other less specific synonyms for this skin disease include acne, summer rash, summer scab, sweating eczema, and saddle scab. No known age, sex, or breed predisposition exists, but horses that are poorly groomed appear to be at increased risk to develop this condition. Incidence usually increases in the spring and summer months, when humidity is higher and horses are shedding their hair coats. Localized disturbance to the normal skin barrier predisposes to infection. Maceration of skin by moisture (water or sweat) and frictional trauma contribute disruption of the normal skin barrier. The areas most at risk are under the saddle and tack, the cervical region, and the distal limbs. The most common bacterial isolates are *Staphylococcus aureus* and *Staphylococcus intermedius*. *Staphylococcus hyicus* is less commonly isolated and

agents and/or antiparasiticide agents, have been used in combination. Fly control is essential to maximize the chances for success in treating and preventing recurrence of cutaneous habronemiasis in horses.

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Bacterial folliculitis due to gram-positive staphylococcal species is seen worldwide. Other less specific synonyms for this skin disease include acne, summer rash, summer scab, sweating eczema, and saddle scab. No known age, sex, or breed predisposition exists, but horses that are poorly groomed appear to be at increased risk to develop this condition. Incidence usually increases in the spring and summer months, when humidity is higher and horses are shedding their hair coats. Localized disturbance to the normal skin barrier predisposes to infection. Maceration of skin by moisture (water or sweat) and frictional trauma contribute disruption of the normal skin barrier. The areas most at risk are under the saddle and tack, the cervical region, and the distal limbs. The most common bacterial isolates are *Staphylococcus aureus* and *Staphylococcus intermedius*. *Staphylococcus hyicus* is less commonly isolated and

may be cultured from lesions of pastern folliculitis. The antimicrobial susceptibility patterns between these three staphylococcal species in the horse are not reported to be substantially different.

Pastern dermatitis—also called *scratches*, *cracked heal*, *grease heal*, *mud fever*, or *mud rash*—is a dermatitis that occurs after trauma to the palmar or plantar aspects of the pastern (see Chapter 4.9: “Pastern Dermatitis”). Chronically moist environmental conditions, long hair, and ectoparasites (mites, *Pelodera*, or *Strongyloides* larvae) also can contribute to the development of this localized form of folliculitis. Infection with bacteria other than *Staphylococcus* spp. and with fungal organisms can occur in pastern folliculitis. Pastern folliculitis also often has associated furunculosis, and scar tissue can form because the infection is often deep.

### Clinical Signs

Early clinical lesions are often more easily palpated than visualized and are characterized by small 2- to 3-mm in diameter foci of erect hairs that project from papules. Lesions can increase in diameter up to 1 cm. Papules often develop central ulceration with a purulent or serosanguineous exudate that results in crust formation. As lesions heal, they become flattened and develop alopecia. Expanding areas of circular alopecia and scale may develop as the infection progresses. Hairs in affected areas may epilate more easily. These lesions are often painful, and horses may resent palpation and saddling. Pruritus is uncommon but, if present or severe, possible concurrent hypersensitivity reactions should also be considered. Nodules with draining tracts and the lesions that indicate furunculosis are much less common but can result in scarring with leukoderma and leukotrichia.

### Diagnosis

Differential diagnoses include dermatophytosis, dermatophilosis, other bacterial pyodermas, and folliculitis (*Streptococcus* spp., *Corynebacterium* spp.), demodicosis, and pemphigus foliaceus. Diagnosis is made based on compatible history (time of year, management concerns such as poor grooming), physical examination findings, and cytologic evaluation of impression smears of any exudate. More challenging cases that have failed to respond to appropriate therapy may require skin biopsies for bacterial and/or fungal culture and for histologic examination.

### Treatment

Treatment should include removal or control of any underlying precipitating factors such as poor-fitting or unclean tack or inadequate grooming. Some cases of staphylococcal folliculitis are self-limiting and resolve within a few weeks without any therapy. Mild cases may respond to topical therapy with povidone-iodine or chlorhexidine-based shampoos. More severe or chronic cases may require systemic antibiotics. In general, most *Staphylococcus* spp. often resist penicillins and tetracyclines. Potentiated sulfonamides are the antibiotic of choice. Trimethoprim/sulfonamide at a dose of 30 mg/kg every twelve hours for 3 to 4

weeks usually resolves staphylococcal folliculitis. Treatment should be continued for 7 to 10 days beyond clinical cure.

### Prognosis

The prognosis for staphylococcal folliculitis is good, but when it is localized to the pastern, staphylococcal folliculitis can be more difficult to resolve.

## DERMATOPHILOSIS

Dermatophilosis or “rain scald” has a worldwide distribution, although the prevalence of the disease varies with geographic location. It is a moist, exudative dermatitis caused by the actinomycete *Dermatophilus congolensis*. *D. congolensis* is a gram-positive, non-acid fast, branching, filamentous bacterium that can cause a superficial bacterial dermatitis in a variety of species in addition to the horse. It is seen more commonly in humid, tropical regions of the world, and the incidence increases during periods of prolonged heavy rainfall.

Normally, the intact stratum corneum and its associated lipid layer provide an effective barrier against invasion by the organism. However, when the skin has prolonged exposure to moisture, it is more susceptible to maceration or trauma. Damaged epithelium must occur for an infection to develop. The natural reservoir of the organism is not known, and attempts to isolate it from soil have been unsuccessful. Exposure to the organism can occur by direct contact with other infected animals, fomites (grooming or tack equipment), or insects. Motile zoospores of *D. congolensis* germinate in a moist defect of the stratum corneum, thus forming a mycelium that proliferates within viable epidermis and hair follicles. An acute inflammatory response composed primarily of neutrophils is induced when the organism invades the viable epidermis. The organism is unable to penetrate the dermis or the neutrophilic inflammation. When the epithelium is restored and the overlying crusts are shed, the bacteria are typically eliminated with the crusts and can survive in crusts shed into the environment for several years, thus remaining a source of future infection for other horses.

### Clinical Signs

Clinical lesions in the acute stage include papules and pustules that develop into suppurative crusted lesions with exudation and matted hair. Alopecia is variable. Horses with long hair tend to develop larger areas of matted hairs and crusts than horses with short hair. Horses with short hair tend to have smaller, crusted papular lesions. If crusts are removed, the underlying epithelial surface is moist, gray to pink, and indurated. When crusts are removed, adherent tufts of hair are usually removed as well. The pattern of the matted hair and crusts are described as having a “paintbrush” appearance. Lesions are found in areas most susceptible to moisture accumulation and trauma, such as the dorsal midline, distal limbs, muzzle, and periorcular regions. Racehorses may develop lesions on the cranial surface of the hind legs in areas where traumatic abrasions from track debris can occur. Areas of nonpigmented skin may be more susceptible to infection. Alopecia and

hyperpigmentation can develop in cases of chronic infection. Affected areas are more likely to be painful than pruritic. Secondary infection with other bacteria, staphylococci, streptococci, or corynebacteria can develop in more chronic cases.

## Diagnosis

Differential diagnoses to consider include dermatophytosis, bacterial folliculitis, pemphigus foliaceus, and drug eruptions. Diagnosis is based on compatible history and clinical signs, cytologic examination of exudate (the lesion's surface or undersurface of a crust), or emulsified crusts, bacterial and fungal cultures and histopathologic examination of skin biopsies. Direct smears can be stained with new methylene blue, Giemsa or Gram's stain. The organism appears as a gram-positive, branching, filamentous bacterium that forms parallel rows of cocci that create a railroad track-like appearance. The organism grows on blood agar but not on Sabouraud's medium or dermatophyte culture media that contain phenyl red indicator. The organism is more easily isolated from acute lesions because chronic lesions are secondarily infected with other bacteria. Incubating culture plates in an environment with reduced amounts of atmospheric oxygen (microaerophilic) may improve the chance of successful cultures. Histologic examination of the crusts is more likely to result in identification of the organism than examination of the epidermis. Consequently the lesions should not be clipped or scrubbed before biopsy, so as to ensure that the crust is included with the submitted sample. A palisade-layer crust, intracellular keratinocyte edema, and neutrophilic epidermal inflammation are common histologic lesions seen in dermatophilosis.

## Treatment

Equine dermatophilosis often is self-limiting, and many cases will resolve without any treatment. Removal of predisposing factors such as moisture, trauma and exposure to infected animals is important for successful treatment and to prevent transmission. Horses should be kept in a dry environment. Loose crusts and hair should be removed by clipping and soaking with either an antiseborrheic (tar or sulfur-containing) or antibacterial shampoo (povidone-iodine or chlorhexidine). Care should be taken not to contaminate the environment with infected hair and crusts. The organism is sensitive to many antibacterial agents. Daily topical therapy may be sufficient for most mild cases. Topical therapy with either 2% to 5% lime sulfur or povidone iodine should be used daily for 7 to 10 days and then twice weekly until lesions have resolved completely. Systemic antibiotics are used in severe, generalized cases. Procaine penicillin (22,000-44,000 IU/kg) given intramuscularly every 12 hours for 5 days usually is effective.

## DERMATOPHYTOSIS

Dermatophytosis is a common, contagious, superficial fungal infection of keratinized tissues—including the superficial epidermis, hair, and, less commonly, hooves. Synonyms include ringworm or "girth itch." Horses of all ages

can become infected with dermatophytes, but young horses are more commonly affected. Although multiple fungal genera are capable of producing dermatophytosis, the majority of infections result from infection with either *Trichophyton* spp. or *Microsporum* spp. *Trichophyton equinum* (var. *equinum* and var. *autotrophicum*) and *Trichophyton mentagrophytes* are the species most commonly isolated from equine infections. *Trichophyton verrucosum*, *Microsporum gypseum*, *M. equinum*, and *M. canis* are potential less common causes of equine dermatophytosis. Most of these fungal species are zoophilic dermatophytes, and transmission requires direct contact with infected animals or contact with infected hair or crusts in the environment. Infected rodents or cats are the most common sources for infection with *T. mentagrophytes*. Cats are also the typical source for infection with the very contagious species *Microsporum canis*, whereas cattle are the source for infection with *T. verrucosum*. *Microsporum gypseum* is a geophilic fungus that inhabits soil. Consequently, culture and speciation may be beneficial in delineating source of infection.

The prevalence of dermatophytosis increases in hot, humid climates or under conditions of close contact in dark, moist environments. In North America, more cases are seen in the fall and winter months. Young animals with no previous exposure lack immunity and are therefore more vulnerable to dermatophytosis. Horses with poor nutritional status or secondary debilitating diseases can be immunocompromised and more susceptible to dermatophytosis. Not all animals exposed to dermatophytosis develop clinical signs. The incubation period is typically between 1 and 4 weeks, depending on environmental temperature and humidity. Spores in the environment can persist for months to years, and contaminated tack and grooming equipment can be modes of transmission between animals.

## Clinical Signs

Hair loss is the most common clinical sign of dermatophytosis. Alopecia results because infected hair shafts are weakened and break more easily and also because hairs within inflamed hair follicles epilate more readily. Lesions are often multifocal, asymmetric, annular areas of alopecia that vary in size from 2 to 4 mm to several centimeters in diameter. Scales and crusts are often associated with the alopecia but inflammation and erythema may be minimal. Papules may be present and are often most noticeable at the advancing edge of lesions. Initial presentation can mimic urticaria with erect hairs in a circular plaque or papular lesion that may exude serum. However, these lesions quickly progress to become well-circumscribed areas of alopecia, scale, and crusting. Once it occurs, hair regrowth starts in the center of the lesion. Areas most commonly affected in the horse include the head, neck, shoulders, and lateral thorax. Skin abrasions or trauma often precede dermatophytosis; lesions consequently are often seen in areas of saddle or girth friction. Horses are only infrequently pruritic with dermatophytosis.

## Diagnosis

Dermatophytosis may be overdiagnosed when annular skin lesions are erroneously assumed to result from

dermatophyte infection. Differential diagnoses include dermatophilosis, bacterial folliculitis, pemphigus foliaceus, or urticaria due to hypersensitivity reactions. Alopecic lesions with minimal scale or crusting should also have the differential diagnoses of telogen effluvium or demodicosis considered. The flat or plaque sarcoid is a differential diagnosis to consider for solitary lesions. Diagnosis may be suspected based on compatible clinical signs and history, but positive growth on dermatophyte culture medium from samples of hair and/or crusts obtained from representative lesions is necessary for the definitive diagnosis. Fungal culture medium requires vitamin enrichment with nicotinic acid to culture *T. equinum*, and it requires thiamine and inositol to culture *T. verrucosum*. Two drops of a commercial multivitamin B complex can be added to a commercial dermatophyte culture medium to provide these additional nutrient requirements. Microscopic examination of hyphae and conidia allows for species identification.

### Treatment

Treatment of dermatophytosis is not always necessary, because cases can be self-limiting and resolve in 1 to 3 months. Based on culture and identification of the species of dermatophyte involved, the source of infection should be identified and eliminated whenever possible. The goals of therapy are to reduce the severity of the skin lesions, prevent transmission to other animals, and reduce environmental contamination. All infected horses should be kept isolated from noninfected horses. The skin around lesions can be clipped, with caution taken to dispose of hair and crusts to minimize contamination of the environment. Those people who handle infected horses also should take care because dermatophytosis is a zoonotic infection that can cause skin lesions in people. All in-contact animals should be treated. Topical fungicidal therapy should be applied daily for 7 to 10 days and then twice weekly until all clinical lesions have resolved.

Therapy may take up to 6 to 8 weeks until all skin lesions resolve. Topical fungicides that can be used to treat dermatophytes in the horse include 3% to 5% lime sulfur, 0.5% to 2.0% chlorhexidine, povidone iodine, 0.5% sodium hypochlorite, and, when available, enilconazole. Lime sulfur is nonirritating and safe, but owners should

be forewarned about the strong unpleasant odor and the potential for discoloring the hair coat. Enilconazole is an imidazole that is not available in the United States. It is available in other countries and is reported to have excellent efficacy against dermatophytes. Captan has been listed as a therapy in the past but should not be recommended, as it is a carcinogen and can produce contact skin reactions in people. Whole body treatment with topical fungicides is usually more efficacious than is focal treatment of localized lesions, as many horses can quickly develop generalized dermatophytosis. Systemic therapy with griseofulvin (100 mg/kg daily for 10 days) has been used to treat dermatophytosis, but the ideal therapeutic dose is not known in the horse, and efficacy is difficult to ascertain because many horses will self-cure in 1 to 2 months. Griseofulvin should never be considered in pregnant mares, as it is a teratogen.

The environment also needs to be disinfected. Stalls, tools, tack, blankets, and grooming equipment should be cleaned with a sporicidal antifungal agent. Povidone iodine, 6% sodium hypochlorite, 5% lime sulfur, benzalkonium chloride, enilconazole, natamycin, or 1% lime plus 1.5% copper sulfate can all be used to treat the environment or equipment.

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## CHAPTER 4.9

# Pastern Dermatitis

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Equine pastern dermatitis—also known as scratches, cracked heels, mud fever, or mud rash in its mild form; grease heel or dew poisoning in its exudative form; and grapes in its chronic proliferative form—is a common dermatologic entity that provides a diagnostic and therapeutic challenge. Similar to the eosinophilic granuloma complex in cats, equine pastern dermatitis (EPD) should be considered a syndrome rather than a diagnosis. Thus in an attempt to minimize patient, client, and practitioner frustration, uncovering an underlying etiology should be pursued before prescribing a course of therapy. Several key concepts in the areas of pathogenesis, testing, and treatment of EPD that may minimize the need to resort to “idiopathic” as a final diagnosis have recently emerged.

### PATHOGENESIS

EPD is a complex syndrome that encompasses many factors in the propagation of disease (Box 4.9-1). To simplify this entity, a classification system similar to that of otitis externa in small animal medicine aids in organizing a concise, thorough diagnostic approach. To achieve a positive therapeutic outcome, addressing the predisposing and perpetuating factors is just as important as treating the primary cause of EPD.

### CLINICAL SIGNS

The lesions of EPD seem to progress in a similar fashion regardless of etiology. The lesions start at the posterior aspect of the pastern and then spread dorsally and anteriorly. A bilaterally symmetric distribution is most common; however, only one limb may be affected. Lesions are more often detected on—but not limited to—nonpigmented pasterns. Varying degrees of pruritus or pain are detected contingent on the underlying etiology.

Three presentations of EPD are described. “Scratches” is the mildest and most prevalent form of EPD with alopecia, dry scales, and crusts that typify this condition. The skin may be thickened, pruritic, and painful to the point of generating signs of lameness. “Grease heel,” the more exudative form of EPD, is characterized by erythema, erosion, alopecia, and serous to purulent crusting dermatitis with accompanying epidermolysis and vasculitis. “Grapes,” the chronic form of EPD, is distinguished by excessive granulation tissue that may become cornified.

With increasing frequency, the author has been identifying pastern leukocytoclastic vasculitis (PLV; photoaggravated vasculitis), a poorly understood clinical entity

of EPD. PLV first affects the medial and lateral aspects and then may progress to involve the entire nonpigmented pastern of mature horses. The lesions are multiple, well-demarcated, circular, painful, erythematous, and exudative, with tightly adherent crusts. Edema of the affected limb(s) and lameness may ensue. Chronic cases may exhibit a rough or warty surface. Typical of the history of PLV, courses of several antibacterial, antifungal, and even low-dose corticosteroid medications have been tried, to no avail.

### DIAGNOSIS

History is always an integral part of a dermatologic work-up—even more so in investigating EPD. As medicaments, liniments, and other home remedies are often applied to the affected area before examination, determining whether the lesion has changed in appearance due to any topically applied substances may be difficult to discern by a simple visual appraisal. Inspection of the environment (standing water/mud, type of bedding, sand, insect burden, etc.) may lead to pertinent recommendations that may eventually minimize or eliminate the need for symptomatic therapy. The presence of other affected horses or affected humans within the stable may direct the investigation toward an infectious or zoonotic etiology (*Chorioptes bovis*, dermatophytosis).

Skin scrapings or acetate tape strip preparations for mites are both simple and cost-effective diagnostic tests to rule out parasitic causes of EPD. In particular, when *Chorioptes bovis* is suspected, it is recommended that all in-contact horses be tested, regardless of whether they have clinical signs, because asymptomatic carriers have been reported to perpetuate the mite infestation. Cytology with DiffQuik or Gram’s stain is another inexpensive and often fruitful test if *Dermatophilus congolensis* (cocci with a “railroad track” orientation) or *Staphylococcus* spp. (engulfed cocci within neutrophils) are suspected. Bacterial culture and sensitivity testing may direct selection of topical/systemic antibiotics.

Fungal culture (DTM and/or Sabouraud’s agar) is the best way to rule out dermatophytosis. Whether the fungal cultures are done in a diagnostic laboratory or in-house, it is imperative that niacin be added to the agar to satisfy growth requirements of *Trichophyton equinum*. In addition to detection of a color change on the DTM medium, identification of the species of dermatophyte (and thus the source of the infection) is paramount to the diagnosis and management of dermatophytosis (see Chapter 4.8: “Folliculitis: Staphylococcal Pyoderma, Dermatophilosis, and

**BOX 4.9-1****Pathogenesis of Equine Pastern Dermatitis****Predisposing Factors****Genetic**

Nonpigmented skin and hair on lower limbs  
Feathers on pasterns  
Keratinization disorder

**Environmental**

Climate/moisture  
Poor stable/pasture hygiene  
Sand, especially Arabians

**Iatrogenic**

Use of irritant topical products  
Training devices  
Poor grooming habits

**Primary Factors****Physical and chemical irritants**

Blistering  
Creosote, motor oil  
Treated bedding/shavings

**Immune-mediated**

Contact allergy  
Photosensitization  
Vasculitis (PLV; purpura hemorrhagica)  
Pemphigus complex

**Infectious**

Dermatophytes/mycetoma  
Spirochetosis

**Parasitic**

*Chorioptes* spp.  
Trombiculidiasis (chiggers)  
*Pelodera strongyloides*  
*Strongyloides westeri* larvae

**Neoplastic**

Sarcoids (fibroblastic, verrucous)

**Perpetuating Factors****Bacterial infections**

*Staphylococcus* spp.  
Botryomycosis  
*Dermatophilus congolensis*  
Fusiform bacteria

**Pathologic skin changes**

Trauma  
Insect bites

**Environmental factors**

Ultraviolet light exposure  
Cold

Dermatophytosis"). Complete blood counts and chemistry profiles are useful in ruling out hepatogenous photosensitization disorders and other metabolic illnesses.

Skin biopsy and dermatopathology should be considered if immune-mediated disorders or neoplastic conditions are suspected. Skin biopsies are also warranted if prolonged, expensive immunosuppressive or chemotherapeutic regimens are anticipated. In the case of PLV, the skin biopsies should be read by a dermatohistopathologist with an interest in equine skin diseases. Acute changes—including leukocytoclastic vasculitis, thrombosis and vessel wall necrosis—are often scarce and can be easily overlooked. Vessel wall thickening and hyalinization, along with epidermal hyperplasia or papillomatosis, may be detected in chronic conditions.

**TREATMENT**

The appropriate therapy obviously involves identification of the predisposing, perpetuating, and primary factors. In general, avoiding pastures/paddocks with mud, water, or sand may minimize predisposing factors. Keeping patients stalled during wet weather and until morning dew has dried is often rewarding. Use of alternate sources of bedding may be beneficial because the chemicals in treated or aromatic types of wood shavings may result in contact dermatitis. Lastly, clip hairs—especially feathers—to avoid moisture retention.

Perpetuating factors should be addressed according to the severity of the condition. The most conservative approach includes cleansing lesions with antimicrobial shampoos (benzoyl peroxides, chlorhexidine, ethyl lactate, imidazoles) twice daily for 7 to 10 days and then tapering in frequency. If a dry environment is not possible, the affected pastern areas can be protected with ointments (creating a moisture barrier); with padded and water-repellent bandages (changed q24-48h); or with Facilitator, a hydroxyethylated amylopectin liquid bandage that is replenished every 1 to 3 days. If the lesions are exudative, astringent solutions—such as lime sulfur (LymDyp), aluminum acetate solutions, black tea bag or sauerkraut poultices, or acetic acid/boric acid wipes (Malacetic Wipes, Dermapet Inc., West Plains, Mo.)—should be used after cleansing.

Topical sprays, creams, or ointments that contain antibiotics, steroids, antifungal agents, or a combination thereof may benefit the patient, depending on the diagnosis. A 2% mupirocin ointment (Bactoderm), with excellent tissue penetration, is the author's preference for addressing localized dermatophilosis and bacterial dermatitis. A DMSO/thiabendazole/sulfa ointment has also been described in the fourth edition of *Current Therapy in Equine Medicine*. If generalized to all four limbs, treatment of the bacterial dermatitis is best accomplished with daily systemic antibiotics (trimethoprim/sulfa 30 mg/kg/day or cephalexin 22 mg/kg q8hrs) until 7 days after clinical resolution.

Lime sulfur dips and chlorhexidine/imidazole-containing shampoos, sprays, and residual leave-on products comprise the current antifungal arsenal in veterinary medicine. Topical enilconazole (Imaverol), labeled for use in horses in various countries other than the United States, has been used to treat fungal infections with reported success. Many veterinary dermatologists feel that systemic griseofulvin lacks efficacy for the treatment of equine dermatophytosis.

Ectoparasiticide therapy consists of avermectins, topical organophosphates (malathion, coumaphos), pyrethroids (permethrin, flumethrin), lime sulfur, and fipronil (Frontline). The latter has had recent success in the treatment of *Chorioptes bovis* within a group of heavier cob and draught-cross horses. Of note was the ability of the parasite to survive off the host, enduring solely in the presence of skin debris in a moist and dark environment and thus emphasizing the need for environmental management to prevent recurrence.

Immunomodulators have been used for the condition. Interferon- $\alpha_{2a}$  given at 1000 IU/ml on a cycle of 1.0 ml per horse daily for 3 weeks and then off for 1 week has been used by the author to help stimulate the local immune defense system, with very little cost or side effects. Immune-mediated conditions such as PLV, however, require a significant immunosuppressive effort to achieve resolution and control of the clinical signs. High-dose glucocorticoids, preferably dexamethasone (0.1-0.2 mg/kg q24h for 7-14 days, then taper over the next 4-6 weeks), along with reduction of UV light exposure by stabling or covering with a light bandage, appears to control—if not resolve—many cases. Should resolution of clinical signs not be achieved by 14 days, the author has achieved excellent results by adding pentoxifylline (PTX), a phosphodiesterase inhibitor. PTX has been reported to have multiple immunomodulatory effects that potentiate the effectiveness of traditional immunosuppressive drugs (i.e., steroid-sparing effect). These include inhibition of lymphocyte acti-

vation and proliferation; increased lymphocyte suppression; suppression of tumor necrosis factor (TNF)- $\alpha$ , lymphotoxin, and interferon- $\gamma$  production; and upregulation of IL-10 mRNA that leads to increased IL-10 serum levels. Oral absorption varies considerably between individuals; thus reported dosages range between 4 to 8 mg/kg every 12 hours.

Once the skin has returned to normal, long-term control of PLV may be achieved by a combination of topical steroids (betamethasone valerate 0.1%, aclometasone 0.05%), coupled with an every other day systemic regimen of PTX and, if necessary, low-dose dexamethasone on an alternate day basis.

The prognosis and healing time of EPD depends on the stage of disease when treatment begins and on the ability to identify the etiology. Ensuring that predisposing, primary, and perpetuating factors are encompassed in a diagnostic and treatment plan will optimize the likelihood of a positive outcome.

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## CHAPTER 4.10

# Equine Sarcoid

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**E**quine sarcoids are the most common skin tumor in horses, donkeys, and mules. They are subclassified into three to six types that are based on physical characteristics and clinical behavior. Occult, or flat, sarcoids are the most benign form and consist of mild scaling and alopecia. Verrucous or warty sarcoids have a raised scaly, lichenified appearance with hair loss and epidermal thickening and may fissure at the skin surface but rarely

ulcerate. Fibroblastic sarcoids are raised subcutaneous masses that are subtyped based on whether the skin surface is affected and include subcutaneous fibroblastic tumors (nodular sarcoids) and ulcerative fibroblastic sarcoids. An additional category—malevolent sarcoids—has been described; these sarcoids appear capable of spreading locally along fascial planes and vessels. Tumors that exhibit multiple subtypes are not uncommon.



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# Equine Sarcoid

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**E**quine sarcoids are the most common skin tumor in horses, donkeys, and mules. They are subclassified into three to six types that are based on physical characteristics and clinical behavior. Occult, or flat, sarcoids are the most benign form and consist of mild scaling and alopecia. Verrucous or warty sarcoids have a raised scaly, lichenified appearance with hair loss and epidermal thickening and may fissure at the skin surface but rarely

ulcerate. Fibroblastic sarcoids are raised subcutaneous masses that are subtyped based on whether the skin surface is affected and include subcutaneous fibroblastic tumors (nodular sarcoids) and ulcerative fibroblastic sarcoids. An additional category—malevolent sarcoids—has been described; these sarcoids appear capable of spreading locally along fascial planes and vessels. Tumors that exhibit multiple subtypes are not uncommon.

## DIAGNOSIS

Historically, histopathologic diagnosis of a sarcoid has required evidence of a well-differentiated fibrosarcoma with pseudoepitheliomatous hyperplasia (elongated rete pegs and epithelial thickening). Because epithelial changes are absent in some subtypes and/or missed in some biopsy sections, sarcoids are occasionally misdiagnosed as fibrosarcomas, neurofibromas, and schwannomas. The use of polymerase chain reaction (PCR) to evaluate for the presence of bovine papillomavirus (BPV) DNA recently has been proposed as an alternative method of diagnosis. Although sarcoids have a benign histopathologic appearance and many appear quiescent, thus causing few problems to affected animal, they should not be ignored. Sarcoids are capable of malignant transformation to more aggressive variants and may begin to grow after many years of apparent senescence. Transformation and increased growth rate are particularly common after unsuccessful treatment, and local recurrence is common.

## EQUINE SARCOIDS AND BOVINE PAPILLOMAVIRUS

Olsen and Cook first suggested the potential role of bovine papillomavirus as an oncogenic virus of equine sarcoids in 1951 while they were studying the transmissibility of cutaneous papillomas. Injection of bovine wart extracts into horse skin created "sarcoid-like" tumors. Papillomavirus-induced oncogenic transformation has been documented in several other species—including rabbits, humans, and cattle. More than 90% of equine sarcoids examined to date contain BPV-1 or BPV-2 DNA, and expression of the BPV-transforming gene, E5, has been found in a small number of sarcoids. Recent data that shows the presence of viral DNA in normal skin of sarcoid-affected horses without evidence of viral gene activation suggests that the virus may be capable of existing in a latent state and becoming activated after some unknown stimuli. Viral latency may explain why sarcoids recur after complete surgical excision and explain their predilection to occur at the site of injury or trauma.

Breed as well as familial and genetic predispositions for development of sarcoid have been documented. Quarter Horses and related breeds are almost twice as likely to develop sarcoid as Thoroughbreds. A direct association between certain equine leukocyte antigen (ELA) alleles and risk for equine sarcoid has been reported; ELA alleles A3 and W13 are strongly associated with an increased risk for sarcoid in Thoroughbreds and in Swiss, French, and Irish warmbloods. The low incidence of the W13 allele in the Standardbred horse population may confer a genetic resistance to sarcoid. Although a clear genetic predisposition for sarcoid exists, the underlying mechanisms that result in this predisposition remain unknown. Specific alleles may confer increased susceptibility to viral infection or may result in a mutation that predisposes to transformation, alters immune surveillance, causes failure to recognize tumor cells.

Although breed and genetic predispositions appear to exist, epidemiologic studies of large herds of donkeys suggest that contact with a sarcoid-affected animal increases the risk of developing a sarcoid in a nonaffected individ-

ual. In one report of an epizootic of equine sarcoid, the increase in incidence occurred approximately one year after importation of a large number of new horses; however, all of the new cases were members of an inbred family. Whether the addition of new horses was significant is unclear. Given the presence of BPV in sarcoid, both infectious and genetic factors may be at work.

Although sarcoids can occur anywhere on the body, sites of predilection include the face (muzzle, ears, and periocular region), distal limbs, neck or ventral abdomen, and areas of previous injury and scarring. Common sites of occurrence vary with geographic location; in the United States, the distal limbs and face are the most common sites. This is in contrast to surveys from Switzerland and England, where the majority of tumors were on the trunk. Whether climatic differences explain these variations is unknown. It has been suggested that fly contact and irritation may affect transmission of these tumors.

## TREATMENT

Numerous publications regarding treatment protocols for sarcoid exist. The number of treatment options reflects the variable efficacy and expense of certain treatments. Accurate success rates are difficult to assess because most studies are not adequately controlled and are based on the population of sarcoids seen at referral centers. Sarcoids treated at referral centers are often the more aggressive types or ones that have recurred after unsuccessful treatment. Horses with sarcoids that remain quiescent or undergo spontaneous regression are rarely presented to referral centers and, consequently, seldom included in clinical trials.

Surgical excision without adjunctive therapy is associated with one of the highest recurrence rates. This rate may be due in part to the fact that fronds of malignant cells may project into the surrounding normal tissue. Because these projections can be infrequent they may be missed on histopathologic review and thus lead to an incorrect assumption of complete excision. Alternatively, surgical trauma and expression of growth stimulatory factors during wound healing may trigger activation of a latent viral infection, thus resulting in new tumor growth.

Laser ablation of tumors has been used to remove or debulk tumor mass, and clinical impression suggests that it may be more successful than conventional surgery. Its improved success may be the result of the ability of the clinician to ablate the wound bed and to destroy any remaining tumor cells. Alternatively, the type of inflammatory response to laser destruction and injury may result in better immune recognition and removal of remaining tumor cells.

Cryotherapy is one of the most commonly used methods for treatment of equine sarcoid. Cryotherapy has its greatest success with veterinarians that use it frequently, and experience with regards to duration and depth of freeze appears to be important for effective response. Thermocouples can be used for more precise measurement of the tissue temperature and depth of freeze. With multiple retreatments the success rate in one study was 85%. A liquid nitrogen spray apparatus can be used; however, depth of freeze is more difficult to control, and multiple treat-

ments are required. In one report, three horses had spontaneous regression of untreated tumors after cryotherapy of another lesion, thus suggesting that destruction of one tumor can result in an immune response against other distant sarcoids.

Hyperthermia has been reported to be successful in a small number of equine sarcoids with spontaneous resolution of some of the non-treated tumors. The increased metabolic rate of tumor cells makes them more heat sensitive compared to normal cells.

Multiple forms of radiotherapy have been used to treat sarcoids. Success rates are generally quite high. Unfortunately, radiotherapy is expensive, requires special equipment and housing, and is potentially hazardous. General anesthesia is required to place radiation implants or to deliver a radiation dose via an external source. These limitations make radiation therapy a difficult and infrequently used method of treatment and confine its use to referral centers.

Several reports on successful treatment of sarcoids using immunotherapy have been published. Immunostimulants that have been used include mycobacterium cell wall extracts, live whole cell bacillus, *Bacillus Calmette-Guerin* (BCG), and propionibacterial cell wall extracts. Living whole cell BCG injections have been associated with anaphylaxis and death and are not currently recommended; purified BCG cell wall extracts or emulsions of whole inactivated organisms have been used with less risk of catastrophic reactions. These products are thought to stimulate cell-mediated immunity, thus leading to recognition of tumor cell-specific antigens and tumor cell destruction. Most immune stimulants require multiple intralesional injections with or without prior cytoreduction (debulking) of the tumor mass. Success rates are reported to be high, with occasional spontaneous regression of untreated tumors especially when regular follow-ups and re-treatments are performed. Recently, successful treatment of sarcoids with compounded topical products has been reported. The distributor of one such product (XXTERRA) claims a 100% success rate with topical application under a bandage. Another compounded agent that contains heavy metal salts and antimetabolites has a reported success rate of 70% in clinical trials at the University of Liverpool. However, to date, no data have been published on either of these agents. Generally these topical products and immune stimulants appear to be most effective against smaller, less aggressive variants of sarcoids.

Intralesional cisplatin in an oily emulsion is reported to have an 87% one-year relapse-free rate for sarcoids. The

repositol effect of the oily emulsion prevents significant systemic levels—thus avoiding systemic toxicity—and maintains effective tissue levels of the chemotherapeutic for prolonged periods of time. A minimum of 4 treatments is recommended; treatment protocols can be expensive, and cytoreduction to decrease the mass of tumor is recommended when treating large tumors. Intralesional tumor necrosis factor (TNF), in combination with xanthine derivatives, has also been used with some reported success.

Topical application of chemotherapeutics—including 5-fluorouracil (5-FU) and a compounded cream-containing heavy metals, 5-FU and thiouracil—have both been reported to be extremely potent in the resolution of sarcoids. Published data regarding the long-term success of these treatments remains unavailable.

With large, aggressive or multiple tumors, a combination of treatment modalities is recommended. At the Veterinary Teaching Hospital at Michigan State University we commonly combine surgical excision or laser ablation with intralesional chemotherapy or radiation therapy. Unfortunately, these combination treatment regimes are expensive and require a significant time commitment from the owner. These combination approaches, in our experience, appear to have the best overall success rate, particularly when treating recurrent or large, aggressive variants of sarcoids. Given the presence and activation of bovine papillomavirus in sarcoid tumors, targeted specific immunotherapy against BPV may be a future option.

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## CHAPTER 4.11

# Nonneoplastic Sterile Nodules

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**S**ingle or multiple noninfectious nodules are a common occurrence in horses. Sterile nodules are either immune-mediated or idiopathic in most cases. The two most common presentations are rapid-onset urticarial lesions and more slowly progressive firm nodules.

### URTICARIA

Urticaria is a very common nodular presentation. Edema in the dermis causes a rapid onset of nodules. This condition is often referred to as “feed bumps” or “protein bumps” by the layperson. The pathogenetic mechanism is that of a type I hypersensitivity most often associated with drug administration such as antibiotics, antiinflammatory agents, or vaccines. Drugs may be administered by any route. Other causes of urticaria include allergies to pollens, foods, or insects. For a large number of cases, no specific agent is identified; these cases are then classified as idiopathic. A portion of idiopathic cases actually are likely to be a form of autoimmune disease that results from autoantibodies cross-linking the Fc receptor of mast cells.

### Clinical Signs

Clinical signs consist of a sudden onset of localized to generalized wheals. The lesions may or may not be accompanied by pruritus. In some horses the lesions take on a serpiginous or ringlike appearance.

### Diagnosis

Diagnosis is usually based on lesion appearance and history of rapid onset. When digital pressure is applied to a lesion, an indentation is made, which supports dermal edema rather than a cellular infiltrate as the cause of the nodule. Biopsy is indicated in cases of recurrent or chronic urticaria and, in severe cases, to rule out vasculitis as a cause for the dermal edema. Occasionally, early dermatophytosis presents with wheal formation. These lesions progress to the more classic dermatophyte lesions in a day or two.

### Treatment

Treatment options depend on the cause and severity of the urticaria. Lesions should regress rapidly on their own on termination of exposure to the initiating antigen. Although antihistamines do not cause regression of existing lesions, they prevent further histamine-binding to receptors while the antigen is still present in the tissue and are therefore

very helpful in cases of urticaria. Hydroxyzine hydrochloride (1 to 1.5 mg/kg q8-12h) is very effective for this condition. Antiinflammatory doses of corticosteroids (prednisolone 0.5 to 1.0 mg/kg/day) may be indicated in severe or chronic cases. In refractory cases, dexamethasone (at an initial dose of 0.02 to 0.1 mg/kg/day followed by oral maintenance dose of 0.01 to 0.02 mg/kg every 48 to 72 hours) may be of benefit. Lastly, epinephrine may be needed if lesions are associated with systemic signs of anaphylaxis.

In addition to treating the urticarial lesions, identification of the underlying cause is paramount. First, with a careful history, drugs should be ruled out. Insect hypersensitivity can be addressed with good fly control by using 2% permethrin. In chronic recurrent urticaria, food allergy should be investigated by placing the horse on grass hay different from the usual hay. If grain is needed, oats should be added while sweet feed and food supplements are avoided. Some horses with recurrent urticaria have positive skin test results to pollens and molds and may benefit from hyposensitization (see Chapter 4.3: “Atopy”).

### Prognosis

Prognosis depends on the underlying cause. When the case can be identified and corrected, prognosis is excellent. Chronic recurrent urticaria is usually idiopathic and therefore has a poor prognosis for cure.

### COLLAGENOLYTIC GRANULOMA

The second clinical presentation of nodules is that of a more slowly progressive, infiltrative lesion. Collagenolytic granuloma (nodular necrobiosis, equine eosinophilic granuloma with collagen degeneration) is the most common nodular skin disease of horses within this category. The etiology of these nodules is unknown; however, it is probably a type IV hypersensitivity reaction to insect bites. Other theories include trauma and atopy as causes for these nodules. Recently, eosinophilic granuloma that arises in areas of previous injection sites has been described and is thought to be a hypersensitivity reaction to the silicone or other component of the coating of hypodermic needles. Thus it appears that multiple etiologies exist.

### Clinical Signs

Collagenolytic granulomas usually occur during the warmer months of the year; however, some stables report occurrence of lesions during the winter months as well. No apparent breed, age, or sex predilection exists. The le-

sions consist of one to several firm dermal nodules that range in size from 0.5 to 5 cm in diameter and usually are located on the sides of the neck, withers, and back. A generalized form consisting of numerous pea-sized nodules on the face, neck, and thorax has been described in Arabian horses. The overlying skin surface and hair coat are usually normal in appearance; however, the surface may ulcerate, especially if it is frequently traumatized by tack. No pruritus or pain is associated with the lesions.

### Diagnosis

The primary differential diagnoses include bacterial furunculosis, fungal granuloma, neoplasia, tick reaction, and hypodermiasis. A definitive diagnosis of collagenolytic granuloma requires biopsy; however, a tentative diagnosis can be made based on history and physical examination. Cytology of an aspirate may be used to help confirm a diagnosis by revealing a primarily eosinophilic inflammation with varying numbers of lymphocytes and histiocytes. No infectious organisms should be identified on cytology or culture.

The primary change on histopathology is an eosinophilic granulomatous reaction that surrounds one to several foci of necrobiosis in which the collagen fibers have an amorphous, granular appearance. In older lesions many of these foci have become mineralized.

### Treatment

Treatment options depend on the number, size, and location of the lesions. Many of the lesions will spontaneously regress with time. Therefore lesions that are not unsightly or are not in a location that is bothersome to the horse can be left alone. Single lesions can be surgically excised. If the horse has only a few lesions, triamcinolone acetonide may be injected intralesionally or sublesionally at 3 to 5 mg/lesion (not to exceed 20 mg total dose). This treatment may be repeated 2 to 3 times at 10-day intervals. Multiple lesions should be treated with oral prednisolone at a dose of 1 mg/kg daily for 10 to 14 days. If lesions respond, the dosage can be slowly decreased over a 2-week period. If lesions recur once corticosteroid therapy has been discontinued, an underlying cause should be pursued. Mineralized lesions will not resolve completely with steroid therapy. The mineralized core can eventually reach the surface but may require surgical excision. Because these lesions are likely a hypersensitivity to insect bites, strict insect control with 2% permethrin spray may help prevent recurrence (see Chapter 4.6: "Fly Control").

## AXILLARY NODULAR NECROSIS

### Clinical Signs

Another less common cause of eosinophilic nodules is axillary nodular necrosis. As the name implies, horses with axillary nodular necrosis present with one or two firm, well-circumscribed 0.5- to 4.0-cm diameter nodules in the subcutaneous tissue of the girth or axillary area. Horses are otherwise healthy, with no clinical signs associated with the condition. The cause of these nodules is unknown.

### Diagnosis

Diagnosis is made primarily based on history and clinical signs. Cytology will confirm the eosinophilic nature of the disease and be similar to that described for collagenolytic granuloma. Histopathology is distinctive; it shows an eosinophilic granulomatous dermatitis with central foci of coagulation but no collagen degeneration. The histologic picture has led to speculation that the nodules arise from a vascular insult, although vascular lesions have not been observed.

### Treatment

Treatment is as described for collagenolytic granuloma—that is, intralesional or sublesional corticosteroids or surgical excision. Similar nodules tend to recur in subsequent years.

## UNILATERAL PAPULAR DERMATOSIS

Unilateral papular dermatosis is a rare idiopathic eosinophilic skin disease of horses. A hypersensitivity reaction is suspected, but the unilateral nature of the disease is puzzling.

### Clinical Signs

No apparent age or sex predilection exists. The disease has been described in a number of breeds; however, Quarter Horses appear to be predisposed. Lesions tend to develop in the warm months and consist of multiple (30-300) papules and nodules that are distributed unilaterally over the trunk. No alopecia or ulceration is associated with the lesions, and they are neither pruritic nor painful.

### Diagnosis

Histopathology is diagnostic and reveals the eosinophilic folliculitis and furunculosis. Hair follicles are filled with eosinophilic debris.

### Treatment

Lesions will spontaneously regress over time; however, systemic corticosteroids will hasten resolution. Lesions may recur in the same or subsequent years.

## STERILE NODULAR PANNICULITIS

Another uncommon cause of infiltrative nonneoplastic nodules in horses is sterile nodular panniculitis. Panniculitis has been described as part of a generalized steatitis in association with dietary deficiencies of vitamin E and/or selenium. In addition, sterile panniculitis in horses seems to exist in a form similar to that described in dogs with sterile nodular panniculitis.

### Clinical Signs

Horses present with multiple deep subcutaneous nodules over the trunk, neck, and proximal limbs that may become fixed to the overlying dermis. Nodules may be painful on palpation. Lesions may drain to the surface and

discharge an oily, sometimes hemorrhagic exudate. Horses may appear systemically ill with fever, anorexia, and weight loss, similar to that in dogs. Anemia has also been seen in association with this disease. Systemic signs may wax and wane with lesion occurrence.

### Diagnosis

Cytology of the exudate shows a pyogranulomatous inflammation with no infectious agents seen. Due to the pyogranulomatous nature of the exudate, an exhaustive search to rule out an infectious etiology is indicated. To obtain a definitive diagnosis, wedge biopsy with aseptic technique should be done to ensure that the biopsy sample is deep enough to visualize the lesion. Tissue should be submitted for bacterial, fungal, and mycobacterial cultures and for histopathology. The sterile nature of the lesion can be confirmed by lack of growth on cultures and failure to find infectious organisms by use of special stains. Histologically, lesions are characterized by diffuse pyogranulomatous panniculitis. Fibrosis may be a prominent feature of chronic lesions. Lymphoid nodules may be present within lesional tissue.

### Treatment

Treatment of sterile nodular panniculitis consists of immune suppressive doses of prednisolone (2 mg/kg/day) or dexamethasone (0.2 mg/kg/day) for approximately 14 days. Corticosteroids are then tapered to the lowest dose that will control the disease. In some cases, lesions can be controlled with a very low dose of dexamethasone once to twice weekly. Upon withdrawal of the glucocorticoid, many horses will relapse.

## CUTANEOUS AMYLOIDOSIS

Cutaneous amyloidosis, a rare cause of nodules in horses, results when amyloid is deposited in the skin and mucosa of the upper respiratory tract. The term *amyloid* describes a group of unrelated proteins that share certain characteristic properties when stained with Congo red and examined under polarized light.

### Clinical Signs

In horses, amyloid may be deposited systemically, thus affecting many organ systems, or in a single organ such as the skin or respiratory tract. Deposition of amyloid in the skin of horses results in the slowly progressive formation of firm, nonpainful cutaneous nodules that range in size

from 0.5 to greater than 10 cm in diameter. Nodules occur most often in the skin of the head, neck, and pectoral regions. Occasionally, nodules may initially develop quite rapidly and resemble urticaria. These initial lesions may then regress, to be followed by a more slowly progressive nodule formation. When amyloid is deposited in the nasal mucosa, clinical signs may include respiratory distress and mild epistaxis.

### Diagnosis

Diagnosis of amyloidosis is confirmed on histopathology of a nodule. Histologically, a nodular to diffuse granulomatous dermatitis with areas of homogeneous, amorphous, eosinophilic material, often surrounding blood vessels, is noted. The presence of amyloid is confirmed by using special stains such as Congo red and by examining the tissue under polarizing light, which demonstrates an apple-green birefringence.

### Treatment

No effective treatment exists for this disease. Corticosteroids may help reduce the size of the lesions initially, probably by decreasing some of the associated inflammation and edema, but this is only temporary. Amyloidosis is a slowly progressive disease.

### Prognosis

The prognosis depends on the degree of respiratory involvement and whether other organs are affected. In humans, some forms of this disease are inherited; therefore, affected horses should not be used for breeding until more is known.

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## CHAPTER 4.12

## Cutaneous Lymphosarcoma

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Clinical manifestations of lymphosarcoma in horses include cutaneous, multicentric, thymic, and alimentary forms. Cutaneous lymphosarcoma can exist as a primary disease entity limited to skin and subcutaneous tissues or concurrently with visceral involvement. Horses of all ages have been diagnosed with lymphosarcoma, with the majority being between the ages of 4 and 9 years. No clear age, sex, or breed predisposition has been identified specifically for the cutaneous form of lymphosarcoma, but some authors have reported a higher incidence in mares. The most common form of cutaneous lymphosarcoma is T cell-rich, B cell lymphoma within the subcutis and dermis. A less common form involving the epidermis with variable extension into the dermis and subcutaneous tissues is termed *epitheliotropic* (cutaneous T cell lymphosarcoma or mycosis fungoides).

## ETIOLOGY

The etiology of equine cutaneous lymphosarcoma is unknown. Although a pleomorphic coryneform bacterium was isolated from the cutaneous masses of two horses, the importance of this isolate is unknown, as no etiologic agent is determined in the majority of lymphosarcoma cases. Inoculation of normal horses with large doses of this organism failed to produce any clinical signs. Virus-like particles were identified by electron microscopy in a foal with multicentric lymphoma. The foal died shortly after birth, and no causal relationship was documented.

## CLINICAL SIGNS

Cutaneous lymphosarcoma can be categorized into T cell-rich, B cell lymphoma or epitheliotropic forms based on the extent of cutaneous infiltration and the cell types involved. T cell-rich, B cell lymphoma defines a mixed population of lymphocytes and reactive histiocytes within the dermis and subcutis. Previously described as *histiolympocytic lymphosarcoma*, several cases have been described recently as T cell-rich, B cell lymphomas through the use of morphologic evaluation, immunophenotyping, and cell proliferation markers. This form of lymphosarcoma is characterized clinically by solitary or multiple well-demarcated dermal and subcutaneous nodules located on any region of the body. These masses are usually covered by haired and intact skin, although they may ulcerate secondary to necrosis as they enlarge. The nodules are typically firm and nonpainful and may vary in size from mil-

limeters to several centimeters in diameter. The cutaneous lesions may appear suddenly, although they more often slowly progress. Spontaneous periods of rapid growth followed by episodes of partial to full remission occur. Concurrent involvement of the nasopharyngeal mucosa may be present in some horses. Such cases may be presented for stridor, exercise intolerance, or nasal discharge.

T cell-rich, B cell lymphoma may demonstrate hormone sensitivity. Partial regression of skin lesions has coincided with hormonal fluctuations associated with the estrous cycle and pregnancy. One report describes a mare that was diagnosed with concurrent cutaneous lymphosarcoma and a granulosa-theca cell ovarian tumor. In addition to cutaneous lesions, aggressive stallion-like behavior and abnormal hormone assay results (elevated serum testosterone and inhibin concentrations) were present in this mare. Progesterone receptors were demonstrated on neoplastic B cells, and temporary regression of the subcutaneous masses occurred following removal of the ovarian mass. Previous partial regression of the subcutaneous lesions in this horse had also coincided with the administration of a synthetic progestin, altrenogest.

Epitheliotropic lymphosarcoma, also known as *mycosis fungoides* or *cutaneous T cell lymphoma*, is infiltration of neoplastic T lymphocytes within the epidermis, with variable extension into underlying tissues. Lesions display varying degrees of ulceration, alopecia, scaling, lichenification, and erythema. Secondary bacterial infection may result in purulent discharge, and pruritus may be present.

Horses with cutaneous lymphosarcoma may also present with weight loss, lethargy, inappetence, intermittent fever, lymphadenopathy, and peripheral edema in addition to skin lesions. Signs of respiratory disease, recurrent colic, weight loss, and/or diarrhea may be observed if concurrent multicentric, thymic, or alimentary forms are present. Exophthalmos, blepharitis, chemosis, epiphora, and conjunctivitis may occur secondary to neoplastic involvement of the periorbital tissues. Careful ocular examinations often reveal infiltration of the palpebral conjunctiva and eyelids, uveitis, corneoscleral and third eyelid masses, as well as retrobulbar involvement.

## CLINICOPATHOLOGIC FINDINGS

Hematologic and biochemical findings in horses with the cutaneous form of lymphosarcoma are often unremarkable. Nonspecific abnormalities may occur with concurrent systemic forms of lymphoma and include anemia,

neutrophilia, hyperfibrinogenemia, hyperglobulinemia, hypoalbuminemia, and hypercalcemia. Leukemia and alterations in peripheral lymphocyte morphology in cases of primary cutaneous lymphosarcoma are rare. A mild elevation of creatine kinase was noted in one report and was attributed to neoplastic infiltration of adjacent muscle.

Serum concentrations of immunoglobulins M, G, and A (IgM, IgG, and IgA) vary in horses with systemic lymphosarcoma and may be elevated or deficient. Selective IgM deficiency has been noted in horses with extracutaneous involvement. However, two recent retrospective studies found that IgM deficiency was neither specific nor sensitive for lymphosarcoma. Monoclonal gammopathies may be noted in horses with diffuse lymphoma. These immunologic changes may not be present in horses with primary cutaneous lymphosarcoma.

## DIAGNOSIS

The differential diagnoses for cutaneous lymphosarcoma include nodular skin diseases—such as nodular necrobiosis (eosinophilic granuloma), mycobacteriosis, hypodermiasis, fibroma, sarcoid, melanoma, chronic urticaria, mastocytosis, fungal granuloma, basal cell tumor, lipoma, panniculitis, and cutaneous amyloidosis. Squamous cell carcinoma and lymphangitis should be considered as diagnostic rule-outs in cases with ulcerative lesions. Definitive diagnosis requires histopathologic or cytologic confirmation. Neoplastic cells have been reported to infiltrate associated fascial and muscle tissue in both T cell-rich, B cell lymphoma and epitheliotropic forms of cutaneous lymphosarcoma. Histopathology is preferred over fine needle aspiration of lymph nodes in cases with peripheral lymphadenopathy because cytology alone may not be definitive. Cutaneous amyloidosis has been reported in horses with lymphosarcoma, including one with cutaneous lymphoma.

Immunophenotyping, or immunohistochemical analysis directed against cell markers, allows for further classification of tumors into B cell or T cell categories. Monoclonal antibodies against surface glycoproteins, surface and cytoplasmic domains, and CD3 and CD5 markers have been used. Epitheliotropic lymphosarcoma in the horse is rare but appears to be of T cell origin. Histiolympathic tumors have been previously classified as B cell or T cell in origin. However, recent work in the morphologic and immunohistochemical classification of equine lymphomas has suggested that the histiolympathic form comprises neoplastic B cells; a concurrent component of reactive but nonneoplastic T cells also exists, thereby classifying these masses as T cell-rich, B cell tumors. Large numbers of nonneoplastic T cells could result in an erroneous diagnosis of a T cell tumor. The role of histiocytes in such masses is unclear. T cell-rich, B cell lymphosarcoma defines neoplastic B cells interspersed within a large population of well-differentiated, benign T cells and variable numbers of histiocytes. Further characterization of T cell subpopulations as CD4 or CD8 in horses with cutaneous lymphosarcoma has not been described.

Hematologic and serum biochemical evaluations are adjunctive diagnostics in horses with cutaneous lymphosarcoma. Ultrasonographic evaluation of cutaneous le-

sions and regional lymph nodes may prove useful in assessment of the extent of neoplastic involvement. A thorough diagnostic examination—including rectal palpation, abdominal and thoracic ultrasonography, abdominocentesis, xylose absorption, thoracic radiography, and transtracheal and thoracocentesis cytology—should be tailored to individual cases for evaluation of internal neoplastic involvement. Endoscopy should be performed to evaluate for nasopharyngeal masses in horses that display upper respiratory signs. Bone marrow aspiration or biopsy may be indicated if leukemia, leukopenia, pancytopenia, or abnormal peripheral lymphocyte morphology are noted. Thorough examination of the reproductive tract and submission of hormone assays (testosterone, inhibin, progesterone) are indicated in mares that display behavioral abnormalities consistent with a granulosa-theca cell tumor.

## TREATMENT

Glucocorticoids remain the mainstay of treatment of cutaneous T cell-rich, B cell lymphoma. Tumor regression is typically noted following the systemic administration of dexamethasone (0.02–0.2 mg/kg IV, IM or PO q24h) or prednisolone (1–2 mg/kg PO q24h). In these authors' experience, dexamethasone proves more effective than prednisolone in treating lymphosarcoma. Once cutaneous lesions have regressed in size and number, the glucocorticosteroid dose can be gradually tapered. However, a rapid decrease or discontinuation of glucocorticosteroid administration may result in recurrence of cutaneous lesions. Relapses are anecdotally reported to be sometimes more refractory to treatment. Long-term maintenance therapy may be required in these cases. These authors prefer to use a dose of 0.04 mg/kg of dexamethasone (approximately 20 mg for an average-size horse) once daily until significant regression of tumors has occurred; the dose then is reduced to 0.02 mg/kg daily and then to every 48 hours. Intralesional injections of betamethasone or triamcinolone can also be performed with success; this may be impractical when presented with a large number of cutaneous lesions. Topical application of corticosteroid preparations may result in clinical improvement in cases with ulceration; however, results of its use have not been reported. In addition to immunosuppression, laminitis is a potential side effect of corticosteroid administration.

Exogenous progestins may demonstrate an antiproliferative effect on lymphosarcoma tumors. The exact mechanism of action has not been determined; however, it is believed to be due to the presence of progesterone receptors, which have been demonstrated on both neoplastic and normal equine lymphoid tissues. Progestogens also have glucocorticoid-like activity, which may also account for the response observed in some cases of lymphosarcoma. In one study, progesterone receptors were identified on 67% of the subcutaneous lymphosarcoma tumors that were evaluated (primarily representing T cell-rich, B cell tumors). In the mare diagnosed with simultaneous cutaneous histiolympathic lymphosarcoma and a granulosa-theca cell ovarian tumor, partial regression of the skin lesions occurred following a ten-day course of the synthetic progestin,



altrenogest (0.044 mg/kg q24h PO). A temporary response was also observed after unilateral ovariectomy. The ovarian tumor stained positive for estradiol and led the authors to believe it was estrogen-secreting. The authors speculated that the steroid hormones secreted by the ovarian tumor may have influenced growth of the T cell-rich, B cell tumors by leading to low progesterone concentrations. Anecdotal reports of tumor regression during pregnancy also exist. In one mare with cutaneous T cell lymphosarcoma, regression of nodules was noted after surgical excision, a single intralesional injection of betamethasone (0.04 mg/kg), and an 8-day course of the oral progestogen, megestrol acetate (0.2 mg/kg q24h). Surgical excision may be efficacious in cases in which a single or a small number of cutaneous nodules exists.

The administration of autologous tumor cell vaccines may benefit horses with cutaneous lymphosarcoma. In one report, tumor regression was achieved by using a combination of low-dose cyclophosphamide and autologous tumor cells infected with vaccinia virus. Cyclophosphamide is thought to potentiate the immune response by decreasing suppressor T cell activity. Infection of tumor cells with the vaccinia virus was performed to augment the host antitumor immune response. The treatment protocol included intravenous administration of cyclophosphamide (300 mg/m<sup>2</sup>) via a jugular catheter over a period of 2 to 3 minutes on days 1 and 36. Immunization with tumor-cell vaccine was performed on days 4 and 21. Response to immunostimulation was confirmed by development of a delayed-type hypersensitivity response to autologous tumor cells injected intradermally in the horse. Potential side effects of cyclophosphamide administration in other species include immunosuppression, enterocolitis, myelosuppression, and hemorrhagic cystitis. No side effects were noted in the horse in this report.

Treatment of epitheliotropic (cutaneous T cell lymphosarcoma) in horses remains speculative because of a paucity of reported cases. Surgical excision of small lesions may be curative. Retinoids and vitamin A analogs inhibit malignant lymphocyte proliferation in human and canine patients with epitheliotropic lymphosarcoma. No reports of the use of retinoids in horses have been published. However, these authors noted no gross or histologic improvement in treating one case of equine epitheliotropic lymphosarcoma with retinoid cream. Side effects included local erythema and signs of irritation after repeated applications.

Investigations as to the effectiveness of radiation ther-

apy and systemic chemotherapy in the management of equine cutaneous lymphosarcoma are needed. Local therapy that consists of intralesional injection of cutaneous nodules with cisplatin has been used successfully in horses with a small number of lesions. Combination chemotherapy that consists of cytosine arabinoside, chlorambucil or cyclophosphamide, prednisone, and vincristine has been reported for use in horses with multicentric lymphosarcoma, as has L-asparaginase.

## PROGNOSIS

Primary cutaneous lymphosarcoma carries a fair to good prognosis; many horses survive for several years. In contrast, cutaneous lymphosarcoma associated with visceral involvement is often rapidly progressive and poorly responsive to therapy, thus resulting in a guarded prognosis for life. The prognosis for horses with extensive epitheliotropic lymphosarcoma remains guarded.

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## CHAPTER 4.13

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# Papillomatosis (Warts)

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Papillomas are one of the most common equine skin tumors. The clinical presentation can be categorized by the distribution of lesions. Three syndromes are recognized—mucocutaneous, haired skin, and pinnae (aural plaques). In the majority of cases, all these syndromes are associated with the presence of papillomavirus. Papilloma viruses are double-stranded DNA viruses that are highly species- and site-specific pathogens of stratified squamous epithelium. Papillomaviruses lack a lipoprotein envelope and are therefore resistant to freezing or desiccation. Formalin, detergents, or high temperatures can reduce infectivity. Natural infection occurs when the virus is introduced into abraded or macerated skin. Because of the resistant nature of the virus, transmission on fomites is possible. Moreover, biting insects may carry the virus between individuals and in some cases may transmit the virus during mating.

### CLINICAL FINDINGS

No breed or sex predilection exists for these neoplasms. Papillomas of mucocutaneous junctions and haired skin typically affect young individuals 1 to 3 years of age, and multiple horses within a group may be affected. Lesions vary from solitary to multiple (often up to 100 individual lesions). The size of individual lesions can vary from 5 mm to 20 mm diameter, and pigmentation may or may not be present. Solitary lesions can often be larger. Aural plaques can occur at any age on the concave aspect of the pinnae and present as depigmented papules or plaques. They can be smooth or hyperkeratotic in appearance. Equine papillomatosis is not generally associated with adverse clinical signs.

### DIAGNOSIS

In the majority of cases the diagnosis is based on the clinical appearance and distribution of the lesions. The disease may be confirmed by histopathologic examination of biopsy tissue and by demonstration of viral particles by immunohistochemistry. Histopathologic findings can vary with the stage of the disease but in general are characterized by focal epithelial hyperplasia. Ballooning degeneration of the cells of the stratum spinosum is present and is accompanied by intranuclear viral inclusion bodies in the stratum spinosum and granulosum. The epidermis becomes chronically more hyperplastic, and rete pegs develop. A lymphocytic inflammatory infiltrate may be pres-

ent. The papillomavirus capsid antigens are well conserved across species, and antibodies directed at these may be used on formalin-fixed tissue to detect the presence of virus.

### TREATMENT

In healthy horses, cutaneous and mucocutaneous papillomas persist for 1 to 9 months before spontaneous remission occurs. Aural plaques do not regress spontaneously. Persistence of lesions other than aural plaques warrants evaluation of the affected individual for concurrent disease or therapy that may compromise the immune system.

Aural plaques are generally not associated with clinical signs, but these pinna lesions may be aggravated by fly bites and secondary infections in the summer months. Repellent fly sprays or other preventive measures against biting insects are indicated to limit both irritation in the affected individual and spread of disease between horses. Secondary infections may be treated with topical antibacterial washes, gels, or creams.

Because of the unsightly nature of equine papillomatosis, owners often seek treatment for their horse. Various therapeutic interventions have been advocated, but no objective studies support these measures. Moreover, because the majority of these lesions spontaneously regress with time, success of a therapeutic agent may be implied—but not proven. Because of the infectious nature of the causative agent, care should be taken to avoid transmission between individuals when multiple horses are stabled or grazed together.

Congenital papillomas have been reported in a small number of neonatal foals. Although the idea has not been proven, transmission of papillomavirus from the dam may occur transplacentally. Moreover, inoculation of the skin from infected sites on the dam during parturition is possible.

Some papillomaviruses have malignant potential. Papillomaviruses are associated with the development of cervical cancer in humans and have been associated with some cases of feline squamous cell carcinomas *in situ*. Although the physical distribution of mucosotropic papillomas and squamous cell carcinomas in horses is similar, papillomavirus antigen has not been detected by immunoperoxidase staining in any squamous cell carcinoma lesions. Bovine papilloma virus, however, has been associated with equine sarcoids (see Chapter 4.10: "Equine Sarcoid").

### Supplemental Readings

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Johnson PJ: Dermatological tumours (excluding sarcoids). *Vet Clin North Am Equine Pract* 1998; 14:625-658.  
 Junge RE, Sunberg JP, Lancaster WD: Papillomas and squamous cell carcinomas of horses. *J Am Vet Med Assoc* 1984; 185:656-659.

## CHAPTER 4.14

# Sporotrichosis

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*East Lansing, Michigan*

### ETIOLOGY

Sporotrichosis is a mycotic disease caused by the dimorphic fungus *Sporothrix schenckii*. *S. schenckii* exists in a mycelial form at environmental temperatures (25°-30° C) and as a yeast form in body tissues (37° C). The organism is distributed worldwide and can be found preferentially in soils that are rich in decaying organic matter. It has also been isolated from barberry and rose bush thorns, sphagnum moss, tree bark, and mine timbers. The handling of stored hay bales has also been associated with outbreaks. The traditionally accepted method of acquiring sporotrichosis is via the inoculation of the infectious organism into tissues. The disease in horses is often associated with a traumatic puncture wound on the distal extremity from a thorn, wood splinter, or barbed wire. Although contamination of a puncture wound by organisms in the environment is considered an important mechanism in acquiring this disease in people as well as horses, contact exposure to cats (especially barn cats) infected with *S. schenckii* is now considered a significant means by which a zoonotic infection can be established. It has also been shown that the claw of the cat may be contaminated with *S. schenckii*, and therefore a direct puncture wound from a claw of a cat needs to be considered a potential source of infection.

### CLINICAL SIGNS

Sporotrichosis can occur in three clinical forms: cutaneous, cutaneolymphatic, and disseminated. In horses, the cutaneolymphatic form is the most common. In most cases, the infectious organism is first inoculated into the dermis or subcutaneous tissue via a traumatic injury. The distal limbs are the most common site for the development of a cutaneous nodule or several nodules. This process extends proximally up the limb and follows the lymphatics, thus resulting in the formation of additional nodules and a "cording" of the lymphatics. Several nod-

ules often become ulcerated and drain a purulent to hemopurulent discharge. In the more chronic cases the ulcerated nodules can develop excessive granulation tissue and take on a "proud flesh" appearance. The proximal draining lymph node may be palpably enlarged and may subsequently ulcerate and drain. Less commonly, the primary cutaneous form of sporotrichosis may be single or multiple intact or draining nodules that develop on the trunk, shoulder, hip, perineum, or face. To this author's knowledge, the disseminated form of sporotrichosis has not yet been reported in the horse.

### DIFFERENTIAL DIAGNOSIS

The initial differential diagnosis for the formation of a cutaneous nodule on the distal extremity should include both bacterial (especially *Corynebacterium* sp., and *Staphylococcus* sp.) and fungal (especially blastomycosis, coccidioidomycosis, cryptococcosis, and histoplasmosis) etiologies. These differentials will vary greatly by regional differences in the incidence of these infections. It is important to obtain the horse's geographic history for at least the past year of travel. However, in the more advanced forms of these diseases, it is very rare for the lymphatics to become "corded" proximally with the formation of additional ascending individual nodules. When individual nodules on the distal extremity become ulcerative, the differential diagnosis should additionally include squamous cell carcinoma, cutaneous habronemiasis ("summer sores"), exuberant granulation tissue ("proud flesh"), and the fibroblastic sarcoid.

### DIAGNOSIS

The most reliable method for confirming the diagnosis of sporotrichosis is to biopsy an intact and nonulcerated nodule and to submit a portion for both histopathologic examination and macerated tissue culture. An 8-mm

### Supplemental Readings

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### DIAGNOSIS

The most reliable method for confirming the diagnosis of sporotrichosis is to biopsy an intact and nonulcerated nodule and to submit a portion for both histopathologic examination and macerated tissue culture. An 8-mm

biopsy punch will give a suitable sample, and the resulting core of tissue can be cut in half longitudinally. Half of the sample should be submitted for histopathologic examination and the other half for culture. It should be requested that the tissue be macerated and cultured for both bacterial and fungal organisms as confirmed cases of sporotrichosis may have a concurrent bacterial component. In instances where only ulcerated and draining nodules occur, the tissue should still be biopsied and sampled as above. This is because both culture and cytologic examination of stained exudate from draining lesions is often negative for the presence of *Sporothrix* organisms. Some cases of equine sporotrichosis are initially negative on macerated tissue culture. In such cases, the histopathology report indicates the presence of a deep pyogranulomatous inflammatory reaction without the presence of any infectious agent upon examination with special fungal stains. In instances in which the lesions continue to persist and do not respond to treatment for any of the bacterial pathogens that are isolated, a portion of the biopsied tissue from a nodule should be submitted to the Centers for Disease Control and Prevention (CDC) laboratory in Atlanta, Ga., for the fluorescent antibody testing (*Sporothrix* antigen-specific direct immunofluorescent antibody test). This procedure is considered the most sensitive test for determining the presence of *Sporothrix* organisms.

## TREATMENT

The treatment of choice for the cutaneolymphatic or primary cutaneous form of sporotrichosis is systemic iodide therapy. The organic iodides have proven superior in efficacy to the inorganic iodides in the treatment of equine sporotrichosis; ethylene diamine dihydroiodide (EDDI Equine) is the drug of choice. This product is in the form of a feed additive and can be mixed with a small amount of grain and administered at a dosage of 1 to 2 mg/kg of the active ingredient given once to twice daily for the first week. The dosage can then be reduced to 0.5 to 1.0 mg/kg once daily for the remainder of the treatment. In general, lesions will begin to regress during the first month of treatment, and treatment should be continued for at least 1 month beyond the complete resolution of all cutaneous nodules and the healing of any ulcerated lesions. Discontinuing therapy prematurely will invariably result in an unnecessary relapse of the disease.

During treatment, the horse should be closely observed for any evidence of iodide toxicity (iodism), which in-

cludes excess scaling and alopecia, serous ocular or nasal discharge, excess salivation, anorexia, depression, coughing, nervousness, or cardiovascular abnormalities. Should any of these signs develop, the treatment should be discontinued for 1 week, and the treatment should be resumed at 75% of the dosage at which the iodism was noted. In most instances, the treatment is subsequently well tolerated. In the rare instances in which iodism is a recurrent problem or the horse fails to respond to treatment with organic iodide, griseofulvin therapy may be used. Griseofulvin has been reported to be effective when administered at a dosage of 20 mg/kg given orally once daily for the first 2 weeks and is then followed by 10 mg/kg given orally once daily for 1 month beyond apparent clinical remission. Itraconazole has also been suggested as an alternative treatment for refractory cases of sporotrichosis. The recommended dosage is 3 mg/kg twice daily mixed with grain, but its expense would be a restriction to its use in most cases.

## PUBLIC HEALTH SIGNIFICANCE

It is important to remember that the accidental inoculation or contamination of broken skin from any contaminated tissues or exudates may infect any person who comes in contact with an animal infected with *Sporothrix* organisms. Several reports have documented the transmission of sporotrichosis to people by contact with a contaminated wound or the exudate from an infected cat.

In some instances, infection has occurred after exposure to an infected cat, although no known preexisting injury or penetrating wound on the person was known before the disease presented. With these considerations in mind, it is advisable that people who handle horses suspected of having sporotrichosis wear disposable gloves. Afterward, they should remove the gloves carefully and wash their forearms, wrists, and hands with either a chlorhexidine or povidone-iodine scrub.

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## CHAPTER 4.15

# Alopecia Areata

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**A**lopecia areata is an uncommon autoimmune dermatosis of horses that is characterized by patches of well-circumscribed, nonscarring alopecia that is grossly noninflammatory. It accounts for 1.33% of the equine dermatoses seen at the Cornell University College of Veterinary Medicine.

### PATHOGENESIS

Alopecia areata is of complex pathogenesis with immunologic targeting of anagen hair follicles by antifollicular antibodies and CD4+ (helper) and CD8+ (cytotoxic) T lymphocytes. IgG autoantibodies are directed against trichohyalin, inner root sheath, outer root sheath, and precortex of the hair follicle. Genetic predisposition may be important in some cases.

### CLINICAL SIGNS

Alopecia areata occurs in many breeds of horses, but Appaloosas and palominos may be at increased risk. No age or sex predilections are apparent. Alopecia areata is characterized by the insidious or sudden appearance of one or multiple well-circumscribed, more or less similar annular areas of noninflammatory alopecia. Lesions vary from 2 to 25 cm in diameter, and the exposed skin appears normal. Lesions are commonly seen on the face, neck, and trunk. Widespread alopecia areata has been called "alopecia universalis." Mane and tail hairs may be lost. Pruritus and pain are absent, and affected horses are otherwise normal. Exposed skin may eventually become hyperpigmented and/or scaly.

At least one form of so-called *mane and tail dysplasia* (dystrophy) is a form of alopecia areata. In this syndrome, focal areas of alopecia and/or short, brittle, dull hairs are present in the mane and/or tail. As this syndrome is particularly common in Appaloosas, genetic predilection may be important in the pathogenesis.

Some cases of so-called spotted leukotrichia with hair loss in the leukotrichic areas may be alopecia areata.

### DIAGNOSIS

The differential diagnosis for more or less annular areas of alopecia includes infectious folliculitides (*Staphylococcus* spp., *Dermatophilus congolensis*, dermatophytes, *Demodex*

mites), occult sarcoid, injection reaction, anagen or telogen defluxion, and follicular dysplasia. The surface changes of scaling and crusting that typically accompany the infectious folliculitides and occult sarcoid are not a feature of alopecia areata. The differential diagnosis for clinically noninflammatory nonpruritic mane and tail hair loss includes follicular dysplasia, selenium toxicosis, *Leucaena* spp. toxicosis, and adverse cutaneous drug reaction.

Definitive diagnosis is based on history, physical examination, and skin biopsy. The characteristic early histopathologic findings include a peribulbar and intra-bulbar accumulation of lymphocytes that has been described as looking like a swarm of bees. These early changes may be quite focal and difficult to demonstrate, thus requiring multiple biopsies from the advancing edge of early lesions and serial sections of these. Later, the histopathologic findings consist of a predominance of telogen and catagen hair follicles, follicular atrophy, and changes consistent with follicular dysplasia (dysplastic hair shafts, distorted hair follicle contours). Miniaturized hair follicles and hairs may be seen. Inflammation may be subtle or absent. Biopsy specimens taken from the center of active lesions or from chronic, static lesions are unlikely to be diagnostic.

### TREATMENT

The prognosis for alopecia areata appears to vary with the distribution of the lesions. Solitary lesions or multiple lesions restricted to one anatomic site often undergo spontaneous remission within several months to 2 years. When hair grows back, it may be finer and lighter in color than normal. Usually these hairs gradually regain a normal diameter and color. Widespread lesions usually persist. However, one horse that had been almost totally alopecic after 12 months of disease made a complete, spontaneous recovery. In another horse, hair loss occurred 3 times (and spontaneously grew again twice) over a period of 3 years.

No curative treatment is currently recognized for alopecia areata. Topical and systemic glucocorticoids have been ineffective. Minoxidil is a vasodilator that possesses hair growth stimulant properties which is useful for the treatment of patchy alopecia areata in humans. Anecdotal reports indicate that the twice-daily topical application of 2% minoxidil solution (Rogaine Hair Regrowth,

Pharmacia & Upjohn, Peapack, N.J.) may be effective in patchy alopecia areata in horses.

### **Supplemental Readings**

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von Tscharner C, Kunkle G, Yager J: Stannard's illustrated equine dermatology notes. *Vet Dermatol* 2000; 11:195-198.

## CHAPTER 4.16

# Linear Alopecia and Linear Keratosis

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*Ithaca, New York*

**L**inear alopecia and linear keratosis are rare dermatoses of unknown cause and are characterized by linear, vertically oriented areas of alopecia or hyperkeratosis, respectively. Linear keratosis accounts for 0.67% of the equine dermatology cases seen at the Cornell University College of Veterinary Medicine. This author's only experiences with linear alopecia are through our telephone consultation and biopsy services.

### **PATHOGENESIS**

The etiopathogenesis of these two conditions is unknown. The lesions do not follow blood or lymphatic vessels, nerves, or dermatomes. Because young—sometimes related—Quarter Horses appear to be at increased risk, genetic predilection may be involved. Clinicopathologically, linear keratosis closely resembles an epidermal nevus (developmental abnormality). Linear alopecia is histopathologically a granulomatous mural folliculitis. It has been speculated that some local dysregulation of keratinocyte function in linear alopecia may allow the keratinocyte to secrete cytokines chemotactic for inflammatory cells. Granulomatous mural folliculitis has been associated with adverse cutaneous drug reactions in other species, and this should be considered in equine linear alopecia as well.

Because both conditions coexist in some horses, it has been suggested that they are variations of the same abnormality. From a histopathologic viewpoint, this is hard to imagine.

### **CLINICAL SIGNS**

Both conditions have been seen in a wide variety of breeds, but Quarter Horses appear to be predisposed. Most

horses develop lesions between 6 months and 5 years of age. No sex predilection is apparent.

Linear alopecia is characterized by the gradual development of annular areas of alopecia, usually in a linear, vertically oriented configuration. One or more linear areas may be present. The lesions are usually 2 to 10 mm wide by a few cm to more than 1 m in length and occur on the neck, shoulder, and lateral thorax. Mild surface scale and/or crust may be present. The lesions are neither painful nor pruritic. Affected horses are typically otherwise healthy.

Linear keratosis is characterized by the gradual, asymptomatic occurrence of one or more unilateral, linear, vertically oriented bands of hyperkeratotic papules that progress to marked hyperkeratosis and alopecia. The lesions vary from 0.25 to 3.5 cm in width by 5 to 70 cm in length and occur most commonly over the neck, shoulder, and lateral thorax. Lesions have also been reported to involve the legs, hip, and pectoral region. Affected horses are typically otherwise healthy.

### **DIAGNOSIS**

These disorders are visually distinctive. External linear trauma, such as those caused by scratches, whip marks, and dripping caustic substances, might be considered differential diagnoses. Histopathologic findings in linear alopecia include early lymphocytic infiltrative mural folliculitis and later granulomatous infiltrative mural folliculitis. Multinucleated histiocytic giant cells are prominent in chronic lesions. Sebaceous glands may be involved, and complete follicular destruction and permanent alopecia is seen in severe chronic lesions. Histopathologic findings in linear keratosis include irregular to papillated epidermal hyperplasia and marked compact orthokeratotic hyperkeratosis. Mild lymphocytic superficial perivascular dermatitis is a variable finding.

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Linear keratosis is characterized by the gradual, asymptomatic occurrence of one or more unilateral, linear, vertically oriented bands of hyperkeratotic papules that progress to marked hyperkeratosis and alopecia. The lesions vary from 0.25 to 3.5 cm in width by 5 to 70 cm in length and occur most commonly over the neck, shoulder, and lateral thorax. Lesions have also been reported to involve the legs, hip, and pectoral region. Affected horses are typically otherwise healthy.

### **DIAGNOSIS**

These disorders are visually distinctive. External linear trauma, such as those caused by scratches, whip marks, and dripping caustic substances, might be considered differential diagnoses. Histopathologic findings in linear alopecia include early lymphocytic infiltrative mural folliculitis and later granulomatous infiltrative mural folliculitis. Multinucleated histiocytic giant cells are prominent in chronic lesions. Sebaceous glands may be involved, and complete follicular destruction and permanent alopecia is seen in severe chronic lesions. Histopathologic findings in linear keratosis include irregular to papillated epidermal hyperplasia and marked compact orthokeratotic hyperkeratosis. Mild lymphocytic superficial perivascular dermatitis is a variable finding.



## TREATMENT

Neither condition is known to undergo spontaneous resolution. Owners should be advised of the potential hereditary nature of these disorders.

Linear alopecia has been anecdotally reported to respond to topical or systemic glucocorticoids, but recurrence is likely. Response to therapy is more likely to be seen in early lesions, wherein complete destruction of hair follicles has not occurred.

Linear keratosis responds poorly to treatment. Topical keratolytic and keratoplastic agents—such as sulfur-salicylic acid-containing shampoos or 50% propylene glycol—can reduce the hyperkeratosis, but their use must be continued for life.

As neither condition is symptomatic, observation without treatment may be an acceptable approach.

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# CHAPTER 4.17

## Pemphigus Foliaceus

SHEILA M.F. TORRES

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DANNY W. SCOTT

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**P**emphigus foliaceus is a rare skin disorder that is characterized clinically by severe crusting and matting of the hair coat. It accounts for only 1.89% of the equine skin disorders seen at the Cornell University College of Veterinary Medicine. It is by far the most common autoimmune skin disease of the horse. No sex or age predilection exists. The age of affected animals has been reported to range from 2 months to 20 years. The disease in horses 1 year old or younger tends to be milder than in older horses, often responds better to treatment, and may spontaneously regress. A breed predilection for Appaloosas has been reported. No geographic distribution or seasonality associated with disease occurrence is known.

The proposed pathologic mechanism involved in lesion formation includes the initial development of autoantibodies against a desmosomal glycoprotein (desmoglein 1). The resultant glycoprotein-antibody reaction causes destruction of the desmosome, thus creating epidermal cell separation known as acantholysis. The detached and separated epidermal cells are called acantholytic keratinocytes. The intraepidermal clefts thus formed are recognized clinically as vesicles, bullae, or pustules.

## CLINICAL SIGNS

Primary skin lesions known as *vesicles*, *bullae*, or *pustules* are rarely seen because they are fragile and rupture easily. The most commonly observed lesions are crusts, scales, erosions with or without epidermal collarettes, exudation,

and alopecia. Over 50% of the cases have varying degrees of edema of the distal extremities and ventrum. The degree of edema may be out of proportion to or occur in the absence of surface skin lesions.

Lesions commonly begin on the face and/or limbs and frequently become generalized within 1 to 3 months. In some cases, lesions can be localized only to the face or coronary bands for long periods of time. Preputial and mammary skin may be targeted in some cases. Occasional horses present with extensive exfoliative dermatitis without distinct, annular, primary or secondary skin lesions. Pruritus and pain are variably present. Systemic signs—including depression, lethargy, poor appetite, weight loss, and fever—may affect more than 50% of the horses. Skin lesions may be exacerbated in warm, humid, sunny weather. Some horses experience spontaneous waxing and waning of their disease.

## DIAGNOSIS

The diagnosis should be based on the history, clinical signs, and the combination of one or more of the following diagnostic tests: cytology, histopathology, and immunopathology.

Impression smears should be made for cytologic examination from intact vesicles, bullae, and pustules, from the exudate underneath crusts, or from recent erosions. The diagnostic findings include the presence of numerous acantholytic keratinocytes, nondegenerate neutrophils,

## TREATMENT

Neither condition is known to undergo spontaneous resolution. Owners should be advised of the potential hereditary nature of these disorders.

Linear alopecia has been anecdotally reported to respond to topical or systemic glucocorticoids, but recurrence is likely. Response to therapy is more likely to be seen in early lesions, wherein complete destruction of hair follicles has not occurred.

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variable numbers of eosinophils, and an absence of microorganisms. Caution is warranted here because rare horses with *Trichophyton* dermatophytosis can have profound acantholysis.

The most reliable diagnostic test is the histopathologic examination of multiple skin biopsies. Subcorneal or intragranular vesicles or pustules with numerous acantholytic keratinocytes are the hallmark of this disease. When found in association with large numbers of neutrophils and variable numbers of eosinophils, these are diagnostic. Here again, rare cases of *Trichophyton* dermatophytosis can produce identical lesions. Thus special stains and fungal cultures may be indicated.

Direct immunofluorescence and immunohistochemistry reveal the deposition of immunoglobulin (especially immunoglobulin G [IgG]) and, occasionally, complement in between epidermal keratinocytes. False-positive and false-negative test results may occur with both immunopathology tests. False-negative test results are often seen when intact primary lesions are not sampled and when animals are receiving or have recently received corticosteroids. Corticosteroids should be discontinued for 3 weeks before immunopathology tests.

The following technique should be used to collect adequate samples for histopathology or immunopathology. Several biopsy samples should be taken from primary lesions (vesicles, pustules) or crusted lesions. The crusts will contain the acantholytic keratinocytes and should be preserved in the sample. The biopsy site should not be scrubbed because this will remove most of the diagnostic material. Samples should be placed in 10% formalin for histopathology and immunohistochemistry and in Michel's preservative for direct immunofluorescence.

Hematologic and serum biochemical abnormalities are inconsistent. More than 50% of the horses manifest some combination of nonregenerative anemia, neutrophilia, hypoalbuminemia, hyperfibrinogenemia, and elevations of serum  $\alpha_2$ ,  $\beta$  and  $\gamma$  globulins.

## TREATMENT

Treatment includes the use of immunosuppressive or immunomodulating agents. Horses younger than 1 year of age often have an excellent response to therapy and may not require any further treatment when the disease is in remission. Older horses have a less favorable prognosis and usually require lifelong maintenance therapy. Advise owners of the need for prolonged and perhaps expensive therapy.

Glucocorticoids and aurothioglucose (Solganal) are the drugs most commonly used to manage equine pemphigus foliaceus. Glucocorticoids can be used as the sole initial therapy or in combination with aurothioglucose. Auro-

thioglucose is rarely used as the sole initial therapy because it may take 6 to 12 weeks before it starts to take effect. It is often used to allow the reduction or discontinuation of glucocorticoids. The recommended dosage for prednisone or prednisolone is 2.2 to 4.4 mg/kg per day orally and for dexamethasone is 0.2 to 0.4 mg/kg per day orally. Some horses appear to respond better to prednisolone than to prednisone. Once clinical remission is achieved with these drugs (usually 10-14 days), the induction dosage is administered every other morning, and the dosage on alternate mornings is reduced by 50% every 2 weeks until the lowest maintenance dose necessary to keep the disease under control is achieved.

Aurothioglucose is initially used as test doses of 20 mg and 40 to 50 mg intramuscularly (IM) 1 week apart to determine whether the drug will be tolerated. Thereafter, induction therapy is initiated at 1 mg/kg IM weekly until a good clinical response is observed at about 6 to 12 weeks. Maintenance therapy is then instituted with injections at 4 to 8 week intervals. Side effects have not been reported in horses but may include stomatitis, dermatitis, blood dyscrasia, and proteinuria. Therefore hemograms and urinalyses should be performed every 2 weeks during induction therapy and every 3 to 6 months thereafter.

Anecdotal evidence suggests that other agents that have been beneficial in some horses with pemphigus foliaceus include azathioprine (2mg/kg orally q24h for induction, then q48h for maintenance), pentoxifylline (10 mg/kg orally q12h), and omega-3/omega-6 fatty acid-containing supplements. These agents would probably be useful in reducing required glucocorticoid doses in some patients.

Pemphigus foliaceus is often worse and more difficult to control in sunny, hot, humid weather. Sun avoidance is very important in such cases.

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## CHAPTER 4.18

## Congenital Skin Disease

STEPHEN D. WHITE

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Congenital skin diseases are uncommon in horses but are often associated with loss of function and with eventual euthanasia of the horse. Because of the suspected genetic nature of these diseases, negative implications exist for any breeding program.

**EPITHELIOGENESIS IMPERFECTA  
(APLASIA CUTIS)**

Epitheliogenesis imperfecta is an inherited congenital discontinuity of squamous epithelium. It is thought to be an autosomal recessive trait and has been reported in several breeds. The lesions (ulcers and erosions) are present at birth and are most common on the distal extremities, head, and tongue. Hooves may slough in severe cases. Clinical presentation is usually diagnostic; confirmation may be obtained by histologic examination of biopsies taken from the margin of the lesions. In moderately to severely affected animals, the disease is fatal within a few days; foals die of septicemia or other developmental abnormalities. Mildly affected areas may heal with scars. The sire and the dam should be removed from breeding programs.

**EPIDERMOLYSIS BULLOSA**

Epidermolysis bullosa (EB) includes a number of diseases typified in human beings by the common finding of blister formation after minor trauma. Most forms are congenital and apparent soon after birth. In animals and in human beings, subsets of EB are classified by the histologic location of the blister or cleft; these are generally near or within the basement membrane zone. These subtypes (and respective cleft location) are termed *EB simplex* (basal cell layer), *junctional EB* (intralamina lucida or basal cell layer), and *dystrophic EB* (sublamina densa).

Junctional EB has been reported in Belgian foals of both sexes and may occur in other breeds, such as the American Saddlebred. It is probably an autosomal recessive disease. Lesions are usually noted within three days of birth and include multiple asymmetric irregular skin erosions and ulcers, which are often encrusted. Lesions may be especially prominent around the coronary bands (thus causing the hoof to crack and slough) and on the oral, anal, and genital mucosa. Collapsed bullae are frequently seen in the oral cavity. Dystrophic teeth are also a feature.

Histology and ultrastructural findings point to a cleft in the intralamina lucida, presumably because of a defect in the anchoring collagen fibrils that connect the base-

ment membrane to the superficial dermis. A laminin-5 defect has been demonstrated in Belgian foals. This disease differs from epitheliogenesis imperfecta in that large areas of the skin are *not* at first devoid of epidermis but rather lose their skin due to the fibril defect. Clinical presentation and the age of the foal are highly suggestive of the diagnosis. Histology and ideally electron microscopy are required to confirm the diagnosis. No treatment is known, and affected horses—as well as the sires and dams of affected horses—should not be bred.

**EQUINE HYPERELASTOSIS CUTIS**

Equine hyperelastosis cutis is an inherited connective tissue disorder. In the United States, it is seen primarily in Quarter Horses and in other breeds with Quarter Horse lineage, such as Appaloosas and Paint horses. Quarter Horses may inherit this disease as an autosomal recessive trait. The age of onset is 0.5 to 2.0 years and depends somewhat on the amount of trauma to which the horse is exposed; sometimes the lesions are not evident until the horse begins training.

Lesions, which may be solitary or multiple, are usually dorsal and consist of easily torn skin, scar tissue, and/or hematomas/seromas. The owner may describe “loose skin” or poor healing of wounds. Distal extremities such as the legs, face, and ventrum are usually spared. Histologic findings are subtle, but “clumped” collagen fibers below the level of the hair follicles may be seen. Poorly oriented collagen fibers are sometimes seen on electron microscopy.

No treatment is known. Affected horses—as well as the sires and dams of affected horses—should not be bred.

**BLACK HAIR FOLLICLE DYSTROPHY**

This rare disease—in which the black hairs grow poorly or not at all—is usually obvious at birth or soon thereafter. White or brown hairs are unaffected. A trichogram (microscopic examination of the black hairs) may show melanin clumping in the hair shaft's cortex and fraying or breaking of the hair shaft itself. Histology shows dysplastic, misshapen follicles with melanin clumping in the follicles, follicular epithelium, and the epidermis as well as melanophages clustered around the base of the hair follicles. No treatment is known, and the genetics of this disease are unknown. Unlike the other diseases noted in this chapter, this disease is cosmetic and does not have implications for function or viability of the horse.

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## CHAPTER 4.19

# Management of Burn Injuries

DEREK C. KNOTTENBELT  
*Liverpool, United Kingdom*

For the purpose of this chapter, burns include thermal burns, chemical burns, and freeze "burns." Thermal burns can be caused by direct fire, heated objects, friction (rope burns), lightning strike/electricity, iatrogenic use of firing and branding irons, and sunburn. Thermal burns are fortunately a relatively rare occurrence in horses. Accidental burns from open fires such as stable or barn fires, where escape is usually impossible, are usually severe and involve large areas of skin.

Sunburn can occur as result of direct exposure to sunlight in pale skinned horses (particularly on the muzzle), but a more significant form is photosensitization. The latter is not really sunburn at all but the ultraviolet light from sunlight causes severe inflammation of nonpigmented skin in the presence of a photosensitizing agent (see Chapter 4.1: Photosensitivity).

Caustic burns are commonly iatrogenic; indeed, caustic skin blistering is regrettably still used in the misguided notion that it has some beneficial therapeutic effect in the treatment of lameness. Accidental caustic burns do occur from contact with strong alkali or acid solutions or with other strong chemicals. Many localized caustic burns arise from use of over-strength topical chemicals. Naturally occurring freeze burn (frostbite) is rare in horses even in the worst climatic conditions. Iatrogenic freeze burns are used to create freeze marks for identification purposes.

### CLASSIFICATION

Burns are usually classified according to the extent of skin involvement and the depth to which the burn penetrates the skin. First-degree burns are superficial and cause localized erythema, pain, and transient edema. Healing is usually uncomplicated without extensive scarring, and although the damage may seem severe, the prognosis is usually good. Serum or plasma exudation is seldom significant. When freezing causes this type of burn, it may damage the melanocytes, thus causing the hair to grow back white.

Second-degree, partial-thickness burns are characterized by vesicle (blister) formation with necrosis and sloughing of the epidermis. Marked pain occurs in the early stages. Exposure of the underlying dermis results in a protracted healing and an inevitable—if minor—scar. Some hair may be lost at the site, but this is usually minor. This injury is used to create a scarring in freeze branding of grey horses where white hair color is less noticeable.

Third-degree, full-thickness burns destroy all the layers of the skin and expose the deeper structures. All local blood vessels in the skin are destroyed along with the hair follicles. Cutaneous sensation is lost, and sloughing and separation of the layers of the skin occurs. Scarring is extensive. This burn is typified by hot branding, in which a permanent scar is the desired consequence. All hair is lost, as is all the normal skin anatomy. The healed site com-

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prises scar tissue alone. This will, of course, eventually contract and remodel, but a permanent defect occurs.

All the various types of burns have the same basic pathology; the prognosis and treatment depends upon the severity (depth) rather than the etiology. The response to burning depends heavily on the temperature and duration of application. Very high temperature flash burns can cause as much damage as lower-temperature burns applied over a longer period. Very dangerous burns can be very small (e.g., an alkali burn of the cornea or exposure of the face to open flames).

The skin of the horse is much more resistant to blistering than that of many other species; thus the effects of even superficial burns may not be obvious for some time after the incident. Furthermore it makes the classification of burns somewhat less useful than it is in humans, in whom the tendency to blister is strong even with superficial burns.

Burns are usually complex, with areas of deeper damage and areas of more superficial nature. Therefore few burns can be simply classified into one category.

The extent of the burn is the second factor in the classification that has a significant bearing on the management and prognosis. Usually this is classified as the percentage of the whole body area that is involved in the burn. A good rule of thumb for the estimation of the body area involved can be calculated from the "Rule of Nine" surface distribution. Each forelimb has approximately 9% of the surface, whereas each hind limb has 18%. The head, neck, thorax, and abdomen each occupy 9% of the total surface area.

Partial or full-thickness burns over more than 10% to 15% of the body surface carry a poor prognosis. Thus a small focal burn from a hot coal or iron may cause much pain and a local scarring but is unlikely to threaten the life of the horse. A generalized (whole-body) burn derived from an electrical accident will affect all tissues (not only the skin); thus the consequences are likely to be disastrous in an animal that survives the initial episode. An extensive burn from a stable fire can quickly cause severe shock and hypovolemia; thus even a limited area can be very dangerous unless it is managed accordingly. Grass fire burns to the limbs usually involve all four limbs, and, in any case, the complications are usually such that the prognosis is hopeless. For the most part, small, localized burns have few systemic effects except where other structures are involved (e.g., the eye, the eyelid, or the distal limb). The assessment of any burn must include a full appreciation of the totality of anatomic involvement. Failure to recognize the tissues can result in a poor outcome, whereas a careful and accurate examination can convert an apparently catastrophic position into a survival case. Furthermore, secondary effects of the incident may occur. A stable fire may result in smoke inhalation—which itself can be fatal—and a caustic burn may encourage the horse to lick at the site, thus causing severe alimentary ulceration. Rope burns (galls) are very difficult to manage and are most common around the legs as a result of tethering or rope tangle. The injury may not be apparent at all apart from the severe pain. The skin becomes progressively drier, undergoes necrosis, and eventually either sloughs or forms an eschar at the site of the damage.

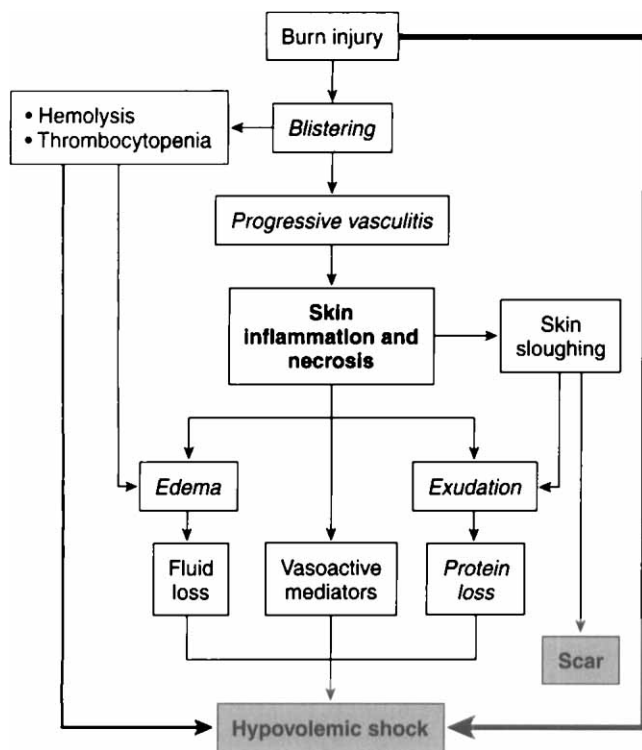
The distribution of the burn will often provide some information on the cause. Burns that involve the face are usually the result of open flame and, more particularly, from sudden flames or explosions. The skin of the eyelids is particularly thin and, along with the cornea, may show the most severe damage. Burns that occur on the back can result from falling flaming or hot wood, for example. Burns on the distal parts of the legs usually arise from ground fires.

Scalding is a particularly difficult type of burn. Water scalding is possibly somewhat less severe than scalding from hot oil or other adherent material that retains heat for a longer period of time. Usually the horse experiences pain from the outset, but the extent of blistering is often slight and may pass unnoticed. The burn continues to cause problems after the incident, and the true extent may only become apparent some days later. Caustic (usually acid or alkali) splashing causes relatively minor burns in the skin, but if splashes get onto the cornea, extreme damage can occur in a few seconds. Scalding injuries and caustic chemicals often produce a flow pattern over the area concerned (e.g., the back).

Intentional iatrogenic burns are of course restricted to the area to which the insult is applied. Firing has for many years been thought to be a beneficial procedure and is still practiced in some parts of the world. The intention is to create local inflammatory response by inducing focal, deep (full-thickness), third-degree burns, and firing is a very good way of doing this. Whether the resulting skin inflammation has any detectable therapeutic benefit in the deeper structures (such as the flexor tendons) is debatable, but the burns are very severe and leave extensive scarring in the pattern chosen by the surgeon. The milder form of the same philosophic therapy is the blister, in which the skin is burnt by chemical applications rather than by heat. As a result, the blister pattern of burn is correspondingly different—diffuse rather than focal. For the most part, this burn results in a superficial (first-degree) burn; thus little or no scarring occurs.

Animals with compromised circulation, such as anaesthetized horses or sick foals, can be burned very easily with heat pads that are intended to provide warmth. These cases can also sustain serious chemical burns from skin antiseptics, alcohol, or even urine if these are left in contact with skin for which the blood supply is compromised either by pressure or by inadequate circulation. In most of these cases no immediate indication of a problem exists. Only when the skin becomes cold and begins to separate does the true extent of the damage becomes apparent.

Healing of burns is always more problematic than a simple wound because some necrosis of the skin can occur and will need to be resolved before healing is possible. Burns appear to be much more susceptible to infection than other forms of wounds; thus infection is a major complication. The presence of necrotic tissue in a wound is a recognized cause of failure of wound healing. Damage to the skin may become obvious quite quickly with the formation of an eschar or sloughing of the affected skin, but the extent of necrosis of deeper tissues—such as tendons and ligaments, bones, and blood vessels—may only become apparent much later in the



**Figure 4.19-1** Primary consequences of a burn injury.

healing period. Iatrogenic burns caused by pin or line firing or branding follow a well-recognized healing course over some weeks or months, and the rest enforced by the treatment may be the real benefit to the horse.

The affected animal must be examined very carefully—not only to establish the full extent and type of the burn but also to establish whether any secondary metabolic consequences from the burn will occur (Figure 4.19-1). The severity usually will be obvious, and the history will help to establish the likely depth and extent. A horse that has been in a stable fire for some time will likely be severely injured and will quickly develop an irretrievable hypovolemic shock unless urgent measures are taken to correct the circulatory needs.

## MANAGEMENT OF THERMAL BURNS

Skin is usually quite slow to absorb heat; as a result, its dissipation also takes much longer than might be expected. Therefore the skin is slow to burn, and the burning effects may continue for some time after the cause has been removed. Furthermore, burn injuries heal very slowly, even in sites where healing is normally good. Therefore the attending veterinarian and the owner must be willing and able to embark upon the process of healing (Figure 4.19-2). The long course inevitably also means a high cost.

All burns should be treated immediately by the application of cold running water, which should be applied for at least 15 minutes. This will reduce the heat retention and limit the consequent necrosis. A protective, water-soluble emollient antibacterial cream should be applied to the burn area. Oil- or fat-based ointments should

be avoided. Silver sulfadiazine (Silvadene) is a very useful topical medication for superficial or partial thickness burns over limited areas.

The metabolic status of the horse must be carefully assessed and supportive measures applied as necessary. These include fluid therapy and, if necessary, an immediate plasma transfusion to ensure that shock is controlled. The loss of plasma is maximal in the first 12 to 24 hours. In all cases, large volumes of intravenous fluid therapy are a useful first emergency measure. This applies particularly to the more severe burns (full-thickness over 5% or more of the body). If the animal is already in a state of shock, aggressive antishock therapy must be instituted immediately. This course of action may include large volumes of balanced electrolyte solutions (e.g., Hartman's solution or lactated Ringer's or even hypertonic [7%] saline). A helpful rule of thumb is that for each percentage body surface involved, 3 to 4 ml/kg body weight should be administered. Fluids should not be sustained if hydration is adequate because it might add to the secondary edema, particularly within the lungs.

Plasma protein estimation may identify falling total protein with albumin loss. Good-quality fresh or preserved plasma will be useful; 1 L of plasma will raise the total protein by about 0.2 g/L in a 450-kg horse. The total volume of plasma required for severe burn cases can be up to 40 L or more over 2 to 3 days. This can usefully be sustained at a low rate for as long as required.

Pain relief in the form of flunixin meglumine (1 mg/kg IV q24h) or phenylbutazone (2 mg/kg q12h) is essential. Pain is often more severe in the more superficial types of burn. Full-thickness burns may not be very painful, but the metabolic consequences of this type of burn are usually more severe.

The topical use of dilute chlorhexidine solution in saline is controversial. Controlling infection is clearly meritorious but may be better performed simply by irrigation. However, burns are particularly liable to infection. Therefore topical water-soluble antibiotic creams may be advisable. Blisters should be left alone for at least 36 to 48 hours. No merit exists in trying to burst or drain these blisters.

Bandaging may be possible in some cases. In such a case, hydrogel should be applied liberally to the site. Burns are usually highly exudative because of the deficit in skin and the loss of cutaneous lipid. Thus an absorbent dressing should be applied. Bandages must be firm enough to provide support without slippage but loose enough as to limit any further vascular compromise. The dressing must not stick to the wound site.

Full-thickness burns must be covered immediately with a protective fluid proof dressing. In an emergency a clear plastic kitchen wrapping can be useful. Ideally, a hydrogel should also be applied directly to the wound site from the outset.

After 24 to 36 hours, the wound can be cleaned and all damaged tissue removed. The clinician should expect further necrosis to develop over the following few days or weeks. At this stage, all hair in the affected area can usefully be clipped. This prevents matting and reduces pain.

Dressings should be replaced frequently over the first few days, and any necrotic tissue should be removed. A calcium alginate dressing (e.g., Algiderm) is a useful ab-



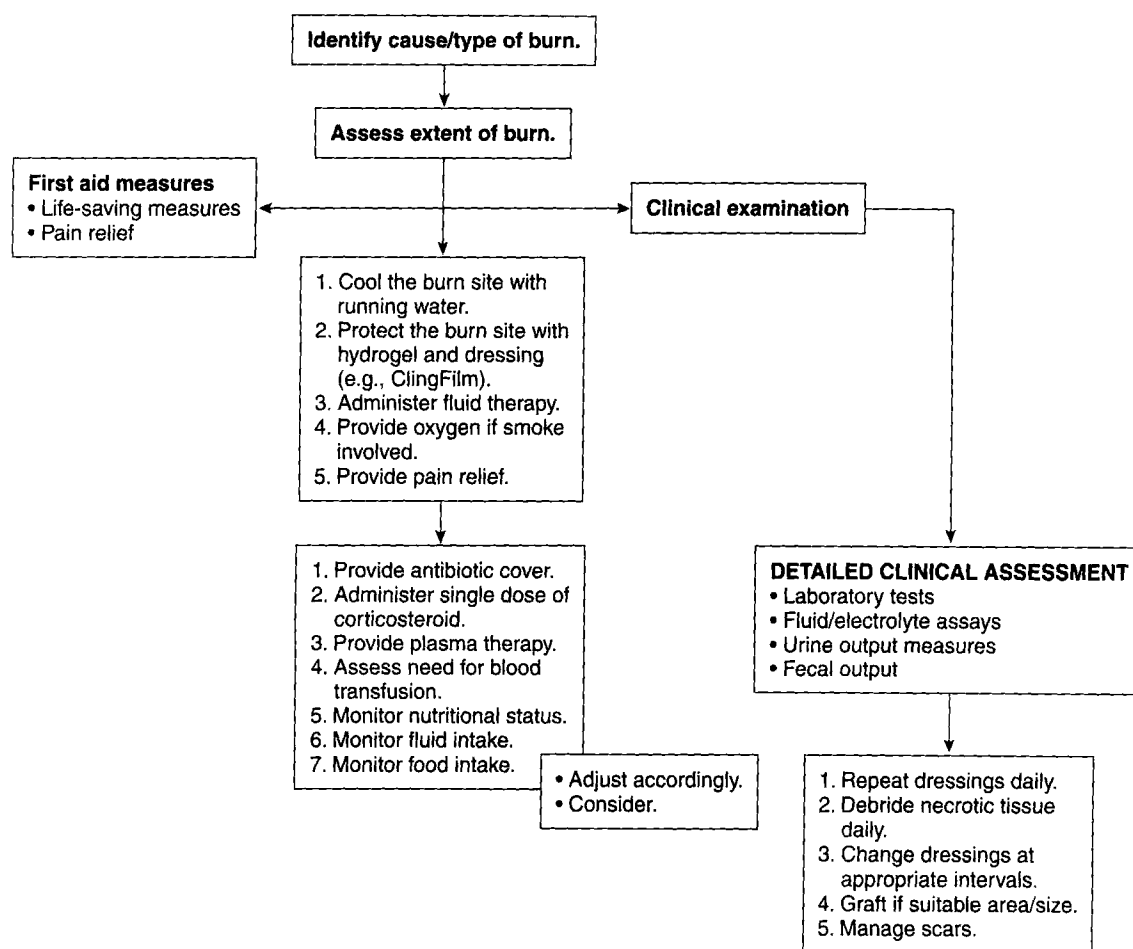


Figure 4.19-2 Clinical protocol for a burn patient.

sorptive dressing that will maintain moist healing conditions at the site. Once healing is underway, the dressings can be left for up to 3 to 4 days, provided that no complications develop. An eschar should be left *in situ* until natural sloughing occurs. While it remains *in situ* it provides an effective biologic cover and protection for the underlying tissues. An overlying moist wound dressing (e.g., a hydrogel [Tegagel]) can sometimes reduce the time taken for the eschar to separate and may also encourage contraction of the healing edges of the wound.

The metabolic status of the horse must be regularly assessed and must include full hematologic profiles for protein analysis and electrolyte status. Hyperkalemia is a common consequence, and seriously burnt horses may show hemoglobinuria. Progressive anemia is a serious potential effect of extensive burns and requires attention as soon as it is recognized. Usually it is caused by a combination of intravascular hemolysis and bone marrow suppression.

The nutritional status of the horse is critical to its recovery. Almost all serious burn cases are in a negative protein balance (i.e., they are losing more than they are absorbing) and have a very much raised energy requirement. The early stages may require parenteral nutritional support, but if the horse will eat, gradual addition of vegetable oil into a high-quality ration (possibly of alfalfa hay) can be helpful.

In cases of extensive skin deficits, skin grafting should

be considered at an early stage—as soon as the granulation tissue is healthy enough to accept a graft. Grafting is unhelpful until all necrotic tissue is removed and the bed of granulation tissue is healthy. Split-thickness, mesh grafts in single sheets or postage-stamp format can be used effectively. Cosmetic grafting with extension flaps, tube grafts, and so on are all techniques that can be applied to the healing of burn injuries of all types. Artificial skin substitutes (e.g., INTEGRA) may be used to protect the exposed tissues and reduce the extent of plasma exudation.

## MANAGEMENT OF CHEMICAL BURNS

Chemical burns usually result in a slow development of dermatitis over the area concerned. Usually the skin is increasingly painful to the touch over the following 24 to 72 hours, and the hair begins to be lost. An exudation develops, and gradually the skin begins to slough. Superficial burns are the most common result from application of over-strength topical medications; on occasion, however, much more aggressive burns can be caused by acids, alkalis, or other inappropriate chemicals (e.g., engine oil, etc.).

The management involves removal of the substance by gentle but copious appropriate washing and then providing suitable topical medications. Clipping the entire affected area so that exudate does not mat into the hair and harbor infection has merit.

## MANAGEMENT OF FRICTION BURNS

Friction burns are usually restricted in area but may be complicated by damage to deeper structures, particularly when they affect the distal limbs. Skin damage is usually more severe than is obvious on first appearance. An area of superficial excoriation may be seen initially. Usually pain is moderate to severe. Serum exudation and possibly bleeding may be present. Progressive skin necrosis occurs with time.

The wounded area must be protected with a moist wound healing gel. Sometimes an antiseptic is used, but the wounds usually are not especially susceptible to infection. Analgesia and dressings are applied until the full extent of the injury is obvious. No merit exists in trying to estimate the extent of the damage.

## MANAGEMENT OF ELECTRICAL BURNS

Electrical burns are almost impossible to treat because the full extent of the damage cannot be assessed. Sometimes the point of contact shows overt skin damage, but even this can be deceptively small. Before examining the horse can occur, the danger of electrical shock absolutely must be eliminated. The horse may require sedation and fluid therapy. Cardiac support may be required. Damage to the central or peripheral nervous system is usually untreatable, although some horses will recover with remarkably few long-term deficits.

## COMPLICATIONS OF BURNS

Infection is a serious and frequent complication of burns and must be addressed at an early stage. For the most part, normal skin commensal organisms such as *Streptococcus equi* var. *zooepidemicus*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* are encountered with some complicated by other gram-negative species, such as *E. coli* and *Clostridia* spp., and yeasts can be found. Silver sulfadiazine (Silvadene) is a useful broad antibacterial that has little or no harmful effects on wound healing.

Some horses suffer from renal shutdown after sustaining a severe burn and renal function must be encouraged and repeatedly checked. Diuretics such as furosemide are often indicated but should be used with considerable care.

Smoke inhalation or internal burns can cause serious pulmonary edema and thus must be controlled. Oxygen supplied directly to the trachea or nasally may be helpful. A single intravenous dose of dexamethasone (0.5 mg/kg) may assist. Intravenous administration of dimethyl sulfoxide (DMSO) at 1 g/kg over the first 2 days may be helpful in reducing the pulmonary edema. All cases in which smoke inhalation has occurred must have systemic antibiotic therapy because the respiratory tract is particularly susceptible to serious infection after inhalation damage. Obtaining a transtracheal aspirate for culture if the chosen antibiotics do not appear to be helping is justifiable. Fungal infections pose a particularly serious threat that may be untreatable.

Corneal and eyelid damage is particularly dangerous because of the delicate nature of the tissue and their intolerance to injury. In cases in which the face has been involved in the burn (to any extent at all) the corneas

should be medicated carefully with artificial tears. In all cases the cornea should be stained with fluorescein to check for ulceration and necrotic tissue. All necrotic tissue should be gently removed with a saline-soaked cotton swab. Under no circumstances should corticosteroids or any strong chemicals such as chlorhexidine or povidone iodine be applied to the eye. Topical antibiotics (e.g., triple antibiotic or gentamicin) should be applied with atropine to control any reflex uveitis. If the eyelids are involved or are suspected to be involved, then particular care must be taken to protect the corneas with artificial tears (applied every hour), and, if necessary, a third eyelid flap can be drawn over the eye to afford sustained protection.

Healing of burn sites is reported to be slower than other types of wounds. This is possibly because the full extent of the injury is not apparent from the outset; furthermore, the damaged tissue is usually slow to separate from the healthy underlying structures. Scarring is inevitable and can be either functionally limiting (e.g., the eyelids or over joints), cosmetically unacceptable, or both. Most serious burn cases have degrees of immunosuppression, which renders them liable to infection and delayed wound healing.

Healing burn sites are often pruritic, and self-inflicted damage can be severe. Suitable sedation may be required (usually acepromazine is effective) to prevent self-inflicted trauma. Cross-tying, neck cradles, or muzzles can also be useful. These measures will require extra nursing observation.

Other complications from burns include colic (usually an impaction) or laminitis. Inappetence or failure to drink are serious potential complications and must be managed early. Fresh green grass is usually a good stimulant to appetite and also provides significant water intake. Caustic burns can result in absorption of the caustic material; thus serious systemic effects may occur.

## PROGNOSIS

The longer the skin was exposed to the burning agent, the worse the damage and prognosis. However, the major factors in the overall prognosis include the severity and the extent of the burn, the structures involved, the care and treatment available, and the extent of secondary complications.

Superficial or limited partial-thickness burns usually heal quite well. Superficial burns often heal without a perceptible scar, but some change in hair color may occur. Scarring is inevitable for deeper burns. Partial- or full-thickness burns that cover more than 10% to 15% of the body carry a poor prognosis, and in over 15%, the outlook is virtually hopeless. The prognosis for full-thickness burns is up to 4 times worse than for superficial burns over the same area. Burns over very limited areas (e.g., rope burns) may be very dangerous if they involve other structures.

Involvement of vital structures can be at least as important as the skin burn. For example, damage to the eyelids can result in loss of the eye from desiccation. Extensive damage to one or more limbs can be disastrous. Extensive scarring can limit the horse's future usefulness and even in some cases the ability to move normally. Proper assessment at the outset may be useful in determining the likely outcome and usefulness; little point exists in subjecting a horse to prolonged treatment if the

likelihood of a favorable outcome is very poor. Nevertheless many cases of amazing recoveries from extreme burns have been reported.

The initial (preburn) health of the horse is important. Weak or debilitated horses have a poor prognosis even with relatively minor burns. Horses with extensive burns require intensive care. Anything less will usually result in a poor outcome. Horses that continue to eat and drink voluntarily have a better prognosis than those that do not.

Shock is a common feature of severe thermal burns, and unless it is controlled, the outlook is poor. Smoke inhalation with or without respiratory tract burns carries a poor prognosis, even with intensive care. Serious infections commonly follow thermal burns (especially those within the respiratory tract). Infections may be impossible to control. Renal failure, severe anemia, and laminitis are common complications in burn patients. Unless these complications can be controlled effectively, the outlook is poor or hopeless.

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# SECTION V

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## Reproduction

*Edited by Dr. Grant S. Frazer*

### CHAPTER 5.1

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## Endometrial Cytology

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**E**ndometrial cytology is an important tool in the complete evaluation of the mare's reproductive tract. Cytologic examination should always be performed when a uterine culture is acquired and when a reproductive problem is suspected. A uterine culture alone may indicate the presence of an organism that may only be a contaminant. Endometrial cytology will define, in many cases, the concurrent presence of an inflammatory response to confirm an active infection. Occasionally an endometrial cytology sample will be nondiagnostic or provide a false-negative result. Such errors may be the result of improper sampling or acquisition early in a disease process.

Many techniques and swabs exist to acquire a sample of fluid/cells to evaluate the uterine environment. The technique used does have some influence on the results, depending on the type of problem. For instance, a localized early uterine infection may be easier to detect when cells from a uterine lavage are examined instead of a uterine swab. Reports have suggested that examination of cells from a uterine lavage is more diagnostic in a subfertile mare than those from a uterine culture swab. Because of its convenience, a single uterine swab is most often used to obtain cells for cytologic examination, especially in an ambulatory practice. If, however, time permits and a uterine lavage is indicated for treatment, the fluid recovered can be useful to confirm swab results.

No matter which technique is used, the mare needs to be properly restrained, the tail wrapped and tied out of the way, and the mare's perineum cleaned. A sterile glove and sterile lubricant should be used. Placement of a sterile sheath or another sterile glove over the culture swab or lavage tubing will help to prevent accidental contamination of the uterus from clitoral, vulvar, or vaginal sources. The veterinarian should avoid contact with the clitoris when placing the tube/swab into the vagina to limit contamination of the reproductive tract.

### USE OF A UTERINE CULTURE SWAB

A number of uterine culture swabs are currently on the market. The two types most frequently used are the McCullough (Barber Veterinary Supply, Richmond, Va.) or the Kalayjian (Barber Veterinary Supply) swab. Both swabs have a guard over one end and the McCullough swab has an internal second sleeve that surrounds the culturette. The McCullough swab has a perforated plastic cap over the end of the swab. On sterile placement of the end of the outer sleeve to the level of the internal cervical os, the inner sleeve is pushed through the perforations and into the uterus. The culture swab is then advanced through the inner sleeve until it contacts the endometrium. The swab should remain in contact with the endometrium for 10 to 15 seconds to allow absorbance of uterine secretions. The calcium alginate swab may be rotated 360 degrees to assist in obtaining cells for cytologic examination. If the clinician rubs uterine swabs on the endometrial surface, the number of red blood cells in a sample will be increased and a reddened area visible on hysteroscopy will occur. Care should be taken not to rotate the swab in both clockwise and counter-clockwise directions, because this may loosen the calcium alginate fibers on the end of the swab. On removal of the swab from the uterus, the end is gently rolled over a sterile glass slide and then transferred to a storage vesicle for transport to the laboratory for bacteriologic identification. Placement of a few drops of sterile saline directly on the culture swab tip before sampling may help to preserve cytologic architecture and will result in a better sample for viewing; however, care needs to be observed to not contaminate the swab. The McCullough swab has the disadvantage that it requires sterile microscope slides so that a single swab may be used for both the cytologic examination and the culture. Alternatively, two swabs may be used; one for cytology and one for culture, but this use may increase iatrogenic contamination of the uterus.

The Kalayjian uterine swab has a removable cap attached to one side of the outer sleeve. On placement of the swab cap to the level of the internal cervical os, the culture swab is pushed through the outer sleeve, which causes the cap to come off the end of the sleeve. The swab is advanced forward and a sample is obtained in a similar manner to the McCullough swab. After the swab is pulled back into the outer sleeve, the entire sleeve with cap is advanced further into the uterus and rotated 360 degrees so that the cap will gently scrape the endometrium. The veterinarian pulls the sleeve back into the vagina with his or her hand covering the cap as soon as it exits the external cervical os to make sure that vaginal cells are not included in the sample. The cap is then cut off the outer sleeve and taped onto a glass microscope slide. The first slide is smeared by using a second slide and is then air dried. The disadvantages of this method are that the outer sleeve has to enter the uterus and possibly increase uterine contamination, and that the cap may scrape the cervical lumen and confound cellular analysis. Before the swab enters the vagina, the entire culture swab may be placed inside a sterile plastic sheath or sterile glove to guard the outer cap against vaginal contamination. The main advantage of this method is that it provides an excellent sample of fluid/cells for examination.

## UTERINE LAVAGE

Uterine lavage is an alternative method to obtain cellular material from the uterus. A uterine lavage tube (Jorgensen Laboratory, Loveland, Colo.) with inflatable cuff is sterilely placed into the uterus at the level of the internal cervical os. Approximately 1 L of sterile saline is infused into the uterus. The veterinarian may gently massage the distended uterus per rectum before recovery of the fluid to increase cell numbers in the sample.

An alternative method of uterine lavage involves the use of an infusion pipette (IMV International, Minneapolis, Minn.) and an attached 60 ml syringe filled with sterile saline. Immediately after the saline is injected into the uterus the veterinarian may manipulate the uterus per rectum and then aspirate as much of the fluid as possible. It is common to retrieve only a small amount (~10 ml) of fluid.

The recovered fluid from either procedure may be treated in one of two ways. One method is to submit the fluid to a diagnostic laboratory for preparation/analysis of the cellular material. Laboratories will use centrifugation, filtration, and automated slide preparation to acquire cells for analysis. Another method involves unit gravity separation. The recovered fluid is placed into a sterile rectal sleeve (large volume) or conical centrifuge tube (small volume). The fluid is allowed to sit for 15 to 20 minutes to allow the cellular material to gravitate to the bottom of the sleeve/tube. The supernatant is removed and the concentrated material at the bottom is placed on a slide, air dried, and stained.

## EXAMINATION OF CELLS

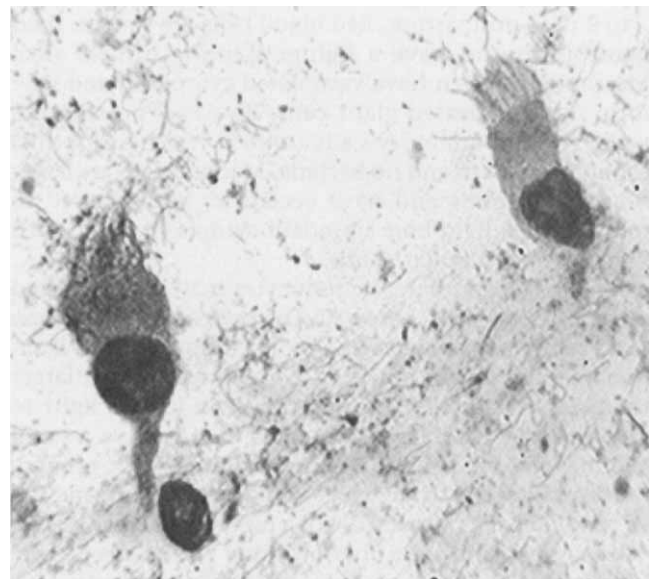
Endometrial cells are most commonly stained with a modified Wright's stain such as Diff-Quik (Fisher Scientific, Norcross, Ga.). Bacteria and fungal elements are easily

seen with this stain. Two slides should initially be made, one stained with Diff-Quik and the other saved for possible staining with Gram's stain. Cellular material on slides should be fixed as soon as practical to retain cellular architecture. Cells may appear degenerative if they are not fixed in a timely manner. Nuclei from degenerate cells may lose spherical shape and become irregular and stain pink because of a decreased affinity for basic dyes. Stains should routinely be filtered (with a coffee filter) to remove debris and decrease artifacts.

Initial assessment of slides should be done under a low power objective (40×) to evaluate the degree of cellularity in the sample and the staining procedure. If only a few cells are present, the sample will not accurately reflect the endometrial environment and the sampling procedure should be repeated. Debris present in the stain or over/under staining may affect interpretation. Usually rafts of endometrial cells surrounded by single cells are visible. If the sample has a good population of cells, assessment of cell types and quantity should then be made under high-power objectives (400× dry, 1000× oil).

A quantitative assessment of the number of inflammatory cells relative to endometrial cells can indicate the presence of inflammation. Guidelines for classification of a cytology sample as inflamed would include more than 5 inflammatory cells per 10 high-power fields (400×) or more than 1 to 2 inflammatory cells per 5 high-power fields (400×) or a ratio of endometrial cells to polymorphonuclear cells of less than 40:1. A ratio may be used with care in samples with low cellularity because the cellular population may not be indicative of endometrial populations. Once the veterinarian becomes familiar with the evaluation of endometrial cytology samples, normal versus inflammatory specimens become easier to evaluate without the need to count absolute cellular numbers.

Endometrial cells may appear cuboidal to columnar with ciliary tufts present on the luminal surface (Figure 5.1-1). Endometrial cells are more cuboidal during anestrus



**Figure 5.1-1** Ciliated columnar endometrial cells (1000× magnification).

and ciliary tufts are present primarily during diestrus. When a mare is treated with prostaglandins the natural cell cycle may be disrupted, and more ciliated cells may be evident during the subsequent estrus. Occasionally, the cilia may become detached during slide processing and cause a significant background artifact. Endometrial cells may appear singularly or as rafts of cells. It has been suggested that rafts are more prominent during diestrus and single cells during estrus, although stage of estrous cannot be determined based on cell type present. Endometrial cell nuclei are located at the base of the cell and may sometimes be disassociated from their cells, probably as a result of smearing during slide processing. Free nuclei are probably one of the most common artifacts of slides prepared by smearing. As an endometrial cell becomes degenerate its nucleus becomes larger and pink as it undergoes karyolysis.

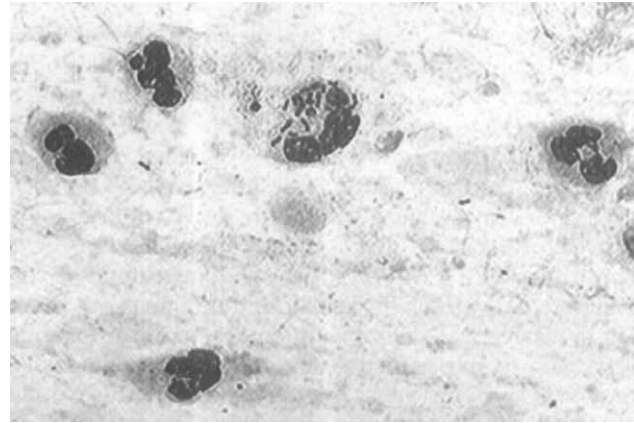
Cuboidal cells may be present from cervical epithelial sources. Use of double-guarded swabs such as the McCullough swab decreases the likelihood of cervical cell contamination. Vaginal cells are usually easily identified as cornified cells with sharp cytoplasmic borders, and they may or may not have pyknotic nuclei present. Mucus from the vaginal epithelium may also confound interpretation of cytology specimens by creating a background artifact.

The most common type of cell on an endometrial cytology slide (other than an endometrial cell) is a neutrophil. Neutrophils will be seen in multiple states of nuclear segmentation. Hypersegmented neutrophils tend to be present with more chronic processes. Degenerative neutrophils have nuclei that are undergoing pyknosis and karyolysis and may indicate the presence of severe inflammation. Neutrophils will appear 2 to 5 hours after an inflammatory insult.

Less commonly, lymphocytes, plasma cells, quiescent macrophages, and activated macrophages may be present, especially with chronic conditions. An exception to this is the postpartum mare in which it is normal to find a significant number of macrophages, red blood cells, and neutrophils. In these mares, neutrophil numbers will decrease and macrophage numbers increase within the first 7 to 9 days postpartum. Red blood cells are smaller than neutrophils and have a lighter staining central area. Macrophages often have vacuolated cytoplasm and may form multinucleated giant cells. By day 9 postpartum very few inflammatory cells (only a few neutrophils) should be present and no bacteria. Macrophages are larger than neutrophils and have eccentric, bean-shaped to round nuclei, light blue abundant cytoplasm, often with vacuoles and granular debris.

In the cycling mare, lymphocytes may be considered normal if only rarely observed. The presence of more than a few lymphocytes indicates a more chronic process. Lymphocytes are usually smaller than neutrophils but larger than red blood cells. They have a thin rim of light to medium blue cytoplasm. The nucleus may have a small dent in what is otherwise a round structure. If the primary inflammatory cell type seen is lymphocyte, lymphatic stasis should be included as part of a differential diagnosis.

Eosinophils have an unknown role within the uterine lumen. It is thought that they are present when there is an impairment or tolerance to the immune system. A sample is considered positive if even a single eosinophil is de-



**Figure 5.1-2** Neutrophils. Center neutrophil has engulfed *Escherichia coli* bacteria (1000× magnification).

tected. Eosinophils have been demonstrated in mares with pneumouterus and urine pooling.

Bacteria and fungi may or may not be phagocytized by neutrophils and macrophages (Figure 5.1-2). Fungi do not require further staining, but a second cytologic slide may be stained with Gram's stain to identify gram-negative versus gram-positive bacteria. These bacteria may prompt the veterinarian to institute antibiotic therapy before the return of culture/sensitivity results.

The inflammatory process may be grossly classified as mild, moderate, or severe, depending on the numbers of cells present and the condition or health of the cells.

Analysis of endometrial samples is best used for acute, active processes in which multiple sequential examinations may demonstrate a uterine response to treatment. The uterine environment is a dynamic, changing environment, and a single cytologic examination may not indicate the direction in which a disease process is progressing. The final step in assessment is to correlate the cytologic findings with culture results and physical examination to complete the diagnostic picture.

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## CHAPTER 5.2

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# Endometrial Culture and Antimicrobial Therapy

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Sampling of the surface of the endometrium for pathogenic microflora is an important part of the breeding soundness evaluation of the mare. Additionally, most breeding sheds and stallion owners require broodmares to have a negative uterine culture before natural mating. Breeds that allow artificial insemination may be less restrictive with this requirement. Other indications for endometrial culture include recent dystocia or retained fetal membranes, detection of intrauterine fluid by ultrasonography, or previously diagnosed endometritis.

### SAMPLING TECHNIQUE

Rectal examination and transrectal ultrasonography to rule out the possibility of pregnancy should always be performed before sampling. Endometrial swabs for culture should be obtained during estrus when at all possible, and obtaining a specimen for cytology at the same time is highly recommended. When mares are sampled during estrus, fewer false-negative culture results are encountered, and cellular morphology of cytologic samples is superior to that obtained during diestrus. In addition, the uterus is more efficient in eliminating bacteria from the caudal tract that may be inadvertently introduced at the time of sampling. A variety of types of uterine culture instruments are commercially available. Guarded culture instruments are preferred because they have a cap or device that shields the swab from exposure to genital tract secretions until the examiner determines that the end of the instrument is within the uterine lumen; this significantly reduces contamination by microflora from the perineum, vestibule, and vagina (see Chapter 1.1: "Neonatal Pharmacology and Therapeutics").

Before a swab for culture is obtained, the tail should be wrapped or placed within a palpation sleeve and tied to the side or held by an assistant. The vulva and perineum should be thoroughly washed with a disinfectant soap, rinsed several times with clean water, and then dried thoroughly. If a rectal exam was performed immediately before perineal preparation, visual inspection of the vestibule for the presence of fecal material is advisable. In mares with poor perineal conformation, lubricant and fecal material is commonly introduced into the vestibule by the examiner's arm running back and forth over the dorsal commissure of the vulva. Removing as much of this as is possible with moist cotton or towels will help reduce the chance that contaminants may be introduced cranially.

Swabs of the endometrium can be taken by introducing the culture instrument through a vaginal speculum or by manual introduction per vaginam. The advantages to obtaining a swab for culturing through a speculum are time efficiency and patient cooperation. Maiden mares may object less to a speculum than to manual introduction. A major shortcoming of this method is the inability to determine whether the end of the instrument is within the uterine body or still within the cervical canal. Manual introduction of the swab requires use of a sterile sleeve and sterile lubrication but also allows the clinician to perform a digital examination of the cervix. Many cervical lacerations, adhesions, or defects can only be diagnosed by digital exploration. It should be noted, however, that evaluation of the cervical integrity is easier when the mare is in diestrus. With either method, avoiding contact of the sterile lubricant with the culture instrument is preferable; the presence of lubricant in the secretions makes interpretation of cytologic samples more difficult. Sterile lubricants labeled as bacteriostatic should not be used; their presence can interfere with recovery of microorganisms. Once the end of the guarded instrument is well within the uterine body and resistance is felt, the swab is introduced through the guarding mechanism and is allowed to remain in contact with the endometrial secretions for 30 seconds. Shorter exposure times may reduce the ability to isolate organisms when low numbers of microflora are present within the uterus.

Immediately after collection of the sample, the swab should be placed into a transport medium system (Culturette and Port-A-Cul Tube, Becton Dickinson Microbiology Systems, Sparks, Md.) and held refrigerated until submission to the laboratory; drying of the swab lessens the likelihood of recovery of potential pathogens. Nutrient types of media should not be used for transport to the laboratory. If possible, samples should be submitted to the laboratory within 2 hours of collection; otherwise they should be refrigerated until submission. Routine processing of swabs includes plating on blood, gram-positive selective (phenylethyl alcohol), and gram-negative selective (MacConkey's or desoxycholate) agars. After initial direct plating, swabs can be placed in an enrichment broth, such as thioglycolate broth, to enhance the recovery of low numbers of organisms. Isolation of anaerobic organisms requires special media such as anaerobic reducible blood agar (trypticase soy base with blood agar). Isolation of *Taylorella equigenitalis*, the causative agent of contagious

equine metritis, requires that swabs be held in Aimes media with charcoal and grown on chocolate agar in 5% to 10% carbon dioxide. Discussion with the laboratory about which antibiotics are routinely included in sensitivity pattern reports is advisable. Often the antibiotics that are useful for treating mares with endometritis may not be the standard ones run by the laboratory. However, if requested at the time of the submission, a specific group of antibiotics can be reported.

### Findings and Interpretation of Results

The most common bacterial pathogens that cause endometritis in mares are *Streptococcus zooepidemicus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*. Other organisms that have been reported with documented cases of endometritis are *Corynebacterium* spp., *Proteus* spp., *Klebsiella oxytoca*, *Bacteroides fragilis*, *Candida* spp., *Aspergillus* spp., and *Staphylococcus* spp. The significance of endometrial culture results should always be interpreted with concurrent endometrial cytology. Positive culture results from a mare with a negative cytology most likely are produced by contamination of the swab, either from the caudal reproductive tract during collection or from airborne environmental contaminants during transfer of the swab to the transport medium system. In these cases, more than one species is often isolated, all with light growth, and the organisms identified are more likely to be commensals of the skin, caudal genital tract, or gastrointestinal tract (e.g.,  $\alpha$ -hemolytic and non-hemolytic streptococci, *Staphylococcus epidermis*, *Enterobacter* spp., and *Streptococcus fecalis*). Likewise, negative culture results from a mare with a positive cytology should be viewed skeptically. Such cases may arise from improper sample handling such as drying of swab, bacteriostatic lubricants, or improper isolation techniques. Although it is possible for a mare to have inflammation in the absence of infection (e.g., inflammation induced by an irritant used for intrauterine therapy), this is the exception rather than the rule, and efforts should be made to definitively rule out endometritis due to the presence of microflora.

Overlap exists among organisms thought to be pathogens and those thought to be contaminants. This underscores the requirement for concurrent vaginal cytology. Without endometrial cytology, the significance of bacteria isolated from uterine swabs is difficult to evaluate. Although contaminants from the caudal tract are the most likely sources of spurious organisms, some reports of commensal organisms that are present in the uterus suggest other sources of positive cultures.

Interpreting uterine cultures without endometrial cytology creates a clinical dilemma. When attempting to certify a mare as "culture clean" for entry to the breeding shed, how should one interpret a culture from a mare that results in isolation of a few colonies of a *Streptococcus* spp. or *E. coli*? If a cytologic examination was performed concurrently and the result was negative, this mare can be sent to the breeding shed as having no evidence of endometritis. Without the cytologic diagnosis, the clinician cannot make such a statement about this mare. The major concern in treating suspect endometritis cases based on cultural findings alone is the potential to create an in-

flammatory response where none existed. Serious infection with resistant organisms becoming established within the uterus is also a risk. A classic example is the induction of fungal endometritis following the indiscriminate use of intrauterine antibiotic therapy. Maiden mares that are treated for *E. coli* based on two colonies and no accompanying cytology specimen can be ruined as potential broodmares by unnecessary antibiotic therapy and irritant intrauterine infusions.

### ANTIMICROBIAL THERAPY

It is imperative that any anatomic defects—such as poor perineal conformation, rectovaginal fistulas, perineal lacerations, and vesicovaginal reflux—be surgically corrected. Without doing so, endometritis will recur despite appropriate antimicrobial therapy. A list of agents used for intrauterine antimicrobial therapy in the mare is given in Table 5.2-1. In most mares, a volume of 50 to 100 ml will

**Table 5.2-1**  
**Antimicrobial Therapy for Intrauterine Use in the Mare\***

Antimicrobial	Dose	Comments
amikacin sulfate	2 g	Gram-negative organisms; buffer with equal volume 7.5% bicarbonate
ampicillin	1-3 g	Broad spectrum ( <i>Streptococcus zooepidemicus</i> )
ceftiofur	1 g	
gentamicin sulfate	1-2 g	Gram-negative organisms; buffer with equal volume 7.5% bicarbonate
kanamycin sulfate	1-2 g	<i>Escherichia coli</i> ; toxic to spermatozoa
penicillin	5 million units	<i>S. zooepidemicus</i>
polymixin B	1 million units	<i>Pseudomonas</i> spp.
ticarcillin	6 g	Broad spectrum
ticarcillin/clavulanic acid	6 g/200 mg	Broad spectrum
nystatin	500,000 units	Antimycotic; must use sterile water (precipitates in saline)
clotrimazole	500 mg	Antimycotic; suspension or cream; q24-48h for 1-2 weeks
vinegar	2%	Antimycotic; 20 ml wine vinegar in 1 L of saline; used as a lavage fluid

\*Parts of this table from Asbury AC, Lyle SK: Infectious causes of infertility. In McKinnon AO, Voss JL (eds): Equine Reproduction, p 384, Philadelphia, Lea & Febiger, 1993; Perkins NR: Equine reproductive pharmacology. Vet Clin North Am Equine Pract 1999; 15:688-689.



give adequate dispersion over the entire endometrial surface. Mares whose uteri are enlarged may require volumes greater than 100 ml to achieve uniform distribution throughout both horns and the body of the uterus. Treatment once daily for 4 to 6 days during estrus is usually adequate for most cases of endometritis. It is often beneficial to precede antimicrobial infusion with uterine lavage, thereby mechanically removing organic debris, which can interfere with the efficacy of most antibiotics. Postpartum mares—or those with an especially enlarged uterus that lacks tone—benefit temporarily from lavage with warm saline before infusion with antimicrobial agents. Oxytocin is an effective tool to enhance uterine clearance of the mare. It is advisable to wait several hours after using any intrauterine antimicrobial agents before administering oxytocin; otherwise, uterine contractions will prematurely expel the antimicrobial agent. In such cases, combining uterine lavage and oxytocin with systemic antimicrobial therapy may prove more efficacious and cost-effective.

The use of systemic antimicrobial therapy is becoming an increasingly popular route for treating mares with endometritis, especially in mares prone to postmating endometritis during the postovulatory period, in mares whose biopsy shows evidence of inflammation deep in the stratum spongiosum, and in mares that receive embryos by transcervical transfer. Trimethoprim/sulfa combinations (30 mg/kg q24h or divided q12h PO) and ceftiofur (4 mg/kg IM q24h) are broad-spectrum antibiotics that should be safe for the early embryo. Enrofloxacin (7.5 mg/kg q24h PO) also has broad-spectrum activity but would not be recommended for use in pregnant or potentially pregnant mares. The bioavailability of the tablet form of enrofloxacin appears to be superior to that of the injectable preparation.

Uterine infections due to fungal or yeast infections are difficult to treat and often follow chronic bacterial en-

dometritis with extensive intrauterine antibiotic use. Clotrimazole and uterine lavage with dilute vinegar solutions are anecdotally the most effective treatments but can require more than one course of therapy. Dilute povidone-iodine lavage solutions (0.05%) have also been suggested. Vaginal speculum examinations are important to monitor cervical inflammation. Some mares are extremely sensitive to even dilute iodine solutions, in which case severe cervicitis, vaginitis, and intraluminal uterine adhesions can result. Occasionally spontaneous recovery from fungal endometritis is seen. In most cases these infections tend to be extremely difficult to resolve; the owner should be given a guarded prognosis for fertility.

### Supplemental Readings

- Asbury AC, Lyle SK: Infectious causes of infertility. In McKinnon AO, Voss JL (eds): *Equine Reproduction*, pp 381-391, Philadelphia, Lea & Febiger, 1993.
- Carleton CL: Clinical examination of the non-pregnant female reproductive tract. In Younquist RS (ed): *Current Therapy in Large Animal Theriogenology*, pp 79-95, Philadelphia, WB Saunders, 1997.
- Madill S, Troedsson MHT: Breeding soundness examination of the mare. In Robinson NE (ed): *Current Therapy in Equine Medicine*, 4th edition, pp 505-512, Philadelphia, WB Saunders, 1997.
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- Troedsson MHT: Diseases of the uterus. In Robinson NE (ed): *Current Therapy in Equine Medicine*, 4th edition, pp 517-524, Philadelphia, WB Saunders, 1997.

## CHAPTER 5.3

# Endometrial Cysts

DALE PACCAMONTI  
*Baton Rouge, Louisiana*

Endometrial cysts are often cited as a cause of infertility; however, a cause-and-effect relationship has not been clearly established. The proportion of mares with endometrial cysts increases with age. Mares over 11 years of age are more than four times as likely to have endometrial cysts as younger mares and a majority of mares over 17 years of age will have endometrial cysts. Reports that associate endometrial cysts with a lower pregnancy rate or increased embryonic loss fail to account for the effect of advancing age. When confounding effects

such as parity and age are controlled for, the assumption that cysts cause infertility is not supported. When confounding factors were accounted for in the analysis of nearly 300 mares, endometrial cysts did not have a statistically significant effect on establishing or maintaining pregnancy, although the time of initial pregnancy diagnosis was not strictly controlled in that study. Another report by a different group of researchers which controlled for the time of pregnancy diagnosis similarly found no difference in pregnancy loss between mares with cysts and

give adequate dispersion over the entire endometrial surface. Mares whose uteri are enlarged may require volumes greater than 100 ml to achieve uniform distribution throughout both horns and the body of the uterus. Treatment once daily for 4 to 6 days during estrus is usually adequate for most cases of endometritis. It is often beneficial to precede antimicrobial infusion with uterine lavage, thereby mechanically removing organic debris, which can interfere with the efficacy of most antibiotics. Postpartum mares—or those with an especially enlarged uterus that lacks tone—benefit temporarily from lavage with warm saline before infusion with antimicrobial agents. Oxytocin is an effective tool to enhance uterine clearance of the mare. It is advisable to wait several hours after using any intrauterine antimicrobial agents before administering oxytocin; otherwise, uterine contractions will prematurely expel the antimicrobial agent. In such cases, combining uterine lavage and oxytocin with systemic antimicrobial therapy may prove more efficacious and cost-effective.

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such as parity and age are controlled for, the assumption that cysts cause infertility is not supported. When confounding factors were accounted for in the analysis of nearly 300 mares, endometrial cysts did not have a statistically significant effect on establishing or maintaining pregnancy, although the time of initial pregnancy diagnosis was not strictly controlled in that study. Another report by a different group of researchers which controlled for the time of pregnancy diagnosis similarly found no difference in pregnancy loss between mares with cysts and

those without cysts, although mares with endometrial cysts tended to have a lower day-40 pregnancy rate.

A quantitative effect of cysts on fertility appeared to exist because an effect was not evident until a mare had numerous cysts or until the cysts were very large. However, even then the effect of endometrial cysts on fertility was much less than that seen with delayed uterine clearance or intrauterine fluid accumulation. A quantitative effect of endometrial cysts could be due to interference with embryonic mobility. It is well known that the equine embryo undergoes a period of mobility after entering the uterus, finally becoming fixed in place at approximately 16 or 17 days' gestation. If mobility is restricted during this period and the embryo is not permitted to contact a sufficient portion of the endometrium, maternal recognition of pregnancy may not occur, thus resulting in luteolysis and embryonic loss.

Rather than being viewed as a cause of infertility, endometrial cysts should be considered an indication of underlying pathologic changes in the uterus. Endometrial cysts are of lymphatic origin, and their occurrence may be associated with a disruption of lymphatic function.

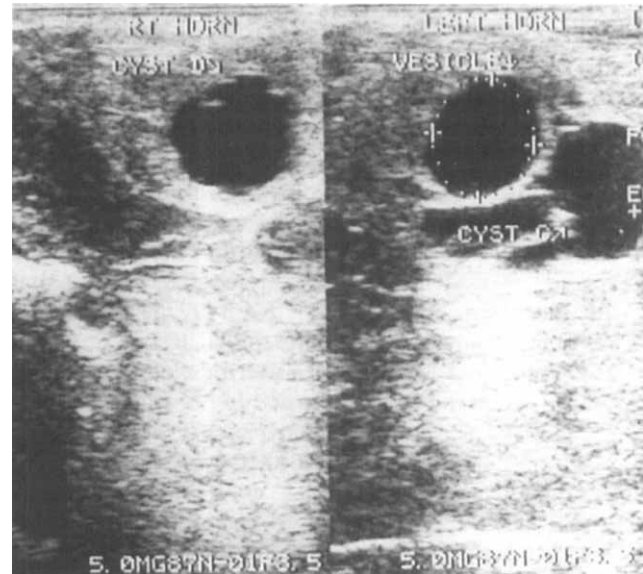
## DIAGNOSIS

Endometrial cysts are best diagnosed with ultrasonography. Cysts can be identified as hypoechoic, immovable structures with a clear border in the lumen of the uterus, as opposed to intraluminal fluid, which is movable and has a less distinct shape or border. Endometrial cysts are usually multiple and are most commonly found at the base of the uterine horns. Cysts may change in size and number between estrus and pregnancy.

Endometrial cysts can complicate early pregnancy diagnosis. Often an endometrial cyst can be similar in size and appearance to an early conceptus. Cysts that appear spherical can often be shown to have a more irregular shape if the ultrasound probe can be reoriented in relation to the cyst. To make early pregnancy diagnosis easier and more reliable, the size and location of endometrial cysts should be recorded with a diagram or by storing ultrasonographic images during a prebreeding examination. Even so, pregnancy examination may need to be repeated or confirmation delayed in some mares with endometrial cysts (Figure 5.3-1).

## TREATMENT

In most cases of endometrial cysts, no treatment is necessary, other than recording their size and location for future reference during pregnancy examination. However, if the cysts are sufficient in size or number to pose a potential threat to embryonic migration, treatment can be



**Figure 5.3-1** Ultrasound image of an early embryonic vesicle and adjacent endometrial cyst.

aimed at facilitating establishment of pregnancy by providing exogenous progestogen.

Progestogen, usually in the form of altrenogest (0.044 mg/kg PO daily), can maintain pregnancy even when the signal for maternal recognition of pregnancy is lacking. Numerous studies have shown the ability of altrenogest to maintain pregnancy after luteolysis or in ovariectomized mares. It should be emphasized that, if progestogen therapy is deemed necessary, the correct dose and frequency of administration is required or the effort is wasted. For example, weekly injections of progesterone in oil or monthly medroxyprogesterone is insufficient to maintain pregnancy and therefore would not be beneficial in mares with large or numerous endometrial cysts.

Alternatively, the cysts may be removed surgically. Laser surgery is an ideal method if the equipment is available. Ligation and transection of the stalk of pedunculated cysts is an alternative. Merely puncturing and draining the cyst or incising its wall will not provide long-term remission.

## Supplemental Reading

Eilts BE, Scholl DT, Paccamonti DL et al: Prevalence of endometrial cysts and their effect on fertility. *Biol Reprod (Monograph Series 1)* 1995; 527.

## CHAPTER 5.4

# Endometrial Biopsy

DALE PACCAMONTI

*Baton Rouge, Louisiana*

An endometrial biopsy is often considered to be a routine part of a complete breeding soundness examination. Because an endometrial biopsy can aid in predicting a mare's chances of carrying a foal to term, the information provided by a biopsy should be considered before purchase or undertaking reproductive surgery such as repair of a cervical tear. Biopsies in some cases provide information that is useful in the diagnosis of infertility and may provide a basis for treatment. It must be realized, however, that an endometrial biopsy alone is not the only—nor usually the most important—piece of information and must be taken in context with other information obtained from the history and reproductive examination.

### PROCEDURE

The perineal area should be thoroughly cleaned for an aseptic procedure. The biopsy instrument is held in a closed position and passed manually through the cervix. Once the instrument is placed into the uterus, the hand is withdrawn from the vagina and placed in the rectum and the tip of the instrument identified. The instrument is then opened and the uterus is pressed through the jaws of the biopsy instrument, and a small portion of an endometrial fold is obtained by closing the biopsy forceps.

Generally, a biopsy specimen is taken from a site at the base of one of the uterine horns. When a biopsy is procured, care should be taken to avoid obtaining tissue from a site near the internal cervical os. Glands are less dense near the cervix, thus making a biopsy obtained from that area less representative of the uterus and more difficult to interpret. Moreover, if the cervix is accidentally biopsied, adhesions can result.

A single biopsy has long been considered representative of the entire uterus; however, studies have shown that variation by as much as an entire category may exist between sites. Therefore, a thorough examination by palpation and ultrasonography should be performed first to determine whether any areas of the uterus appear to be abnormal. If an abnormal area is detected, biopsies should be obtained from both the abnormal and normal areas. Repeated or multiple biopsies do not significantly affect fertility. A mare may become pregnant when bred just a few days after a biopsy specimen is taken.

Biopsies may be taken at any time during the year or during any stage of the estrous cycle, because the mare's cervix is easily dilated. Some recommend taking a biopsy during diestrus for diagnostic purposes because the endometrium is under the influence of progesterone and the glands have achieved maximum tortuosity. Others rec-

ommend taking a biopsy during estrus when the cervix is relaxed and the biopsy instrument is most easily passed into the uterus. Either way, it is important to relay all pertinent history, including the stage during which the biopsy was taken, to the pathologist who reads the biopsy. Periglandular fibrosis may appear worse in biopsies taken during anestrus because of the sparseness of glands. In addition, biopsies taken during anestrus or transition may have evidence of increased inflammation because the cervix has been in a relaxed state for a prolonged period due to the absence of progesterone.

### CLASSIFICATION

Endometrial biopsies are classified into four categories (I, IIA, IIB, III) based on the classification system of Kenney and Doig (1986; see readings list). A mare with a Category I biopsy has an essentially normal endometrium. The likelihood of her becoming pregnant and carrying a foal to term, which is estimated at 80% to 90%, depends more on broodmare management than on the mare's inherent fertility. Mares with a Category III biopsy have severe pathologic changes in the endometrium and an estimated 10% chance of carrying a foal to term, even with good breeding management. Most mares will be classified as a Category IIA or IIB, with an estimated 50% to 80% and 10% to 50% chance, respectively, of carrying a foal to term. This reflects a combination of management practices and the mare's inherent fertility.

Thorough descriptions of the pathologic changes have been published and can be reviewed, but in most cases a pathologist associated with the service that processes the sample will read the biopsy. Even so, if the practitioner can review the biopsy slide it can be helpful in developing recommendations.

A complete histopathologic description is usually provided by the pathologist. However, of primary concern to the practitioner is the severity and distribution of inflammation and degenerative changes—including periglandular fibrosis, angiogenesis and lymphatic lacunae. Degenerative changes carry a worse prognosis than inflammatory changes because they are considered to be permanent and progressive. No treatment for these conditions has been identified. The cause of such degenerative conditions is not known, although it is presumed by many to be due to repeated insults to the uterus. They are more commonly seen in older mares. Dilated lymphatics often indicate a uterine clearance problem. However, delayed clearance is more reliably diagnosed by ultrasonographic examination in the postmating period.

Although biopsy can reveal the presence of an inflammatory condition, other methods (such as examination of perineal conformation) must be employed to reveal why the condition is present, and a culture is needed to identify the particular pathogen. A repeat biopsy after appropriate therapy may reveal the degree of success of treatment.

### Supplemental Readings

Adams GP, Kastelic JP, Bergfelt DR et al: Effect of uterine inflammation and ultrasonically-detected uterine pathology on fertility in the mare. *J Reprod Fertil* 1987; 35(Suppl):445.

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Schoon D, Schoon H-A, Klug E: Angioses in the equine endometrium: pathogenesis and clinical correlations. *Pferdeheilkunde* 1999; 15:541.

## CHAPTER 5.5

# Persistent Mating-Induced Endometritis

MICHELLE M. LEBLANC

*Gainesville, Florida*

**C**urrent knowledge of the etiology and pathophysiology of persistent mating-induced endometritis has evolved over 30 years, but the most significant advances as regards the inciting causes and treatment modalities have happened in the last 10 years. The disease is likely caused by a continuum of degenerative uterine changes that occur in response to aging and parity. A defect in myometrial activity appears to be the primary cause. However, other pathologic uterine findings—such as lymphatic lacunae, angiopathies, and periglandular fibrosis (endometriosis)—contribute to its severity. Genetics may predispose some mares to endometritis. Breeding management and treatment strategies for mares with endometritis should be tailored to each individual and depend on reproductive history, external and internal genital conformation, age, parity, and results of uterine cytology, culture and biopsy.

### PATHOPHYSIOLOGY

Studies in the late 1980s provided strong evidence that a delay in the physical clearance of fluids from the uterine lumen after breeding is associated with infertility in pluriparous mares. Mares susceptible to endometritis accumulate fluid in the uterine lumen and do not clear a bacterial inoculum or nonantigenic markers that are infused into the uterus during estrus. By contrast, fertile mares clear the infused compounds and do not accumulate fluid. Mares that exhibit a delay in uterine clearance appear to have an intrinsic defect in the myometrium, such that the muscle has lost its ability to contract properly after bacte-

rial inoculation or after breeding. Mares with delayed uterine clearance exhibit a decrease in the intensity and the duration of uterine contractions and have a delayed response to uterine infection in comparison to fertile mares. The cause of the defect is not known.

Other factors that contribute to a mare's inability to clear the uterus include increasing age and parity that coincides with a lengthening of the vulva and cranial tilting of the vulva. The changes are likely a consequence of repeated pregnancies, loss of body condition, and genetics. Loss of the structural support of the caudal reproductive tract and stretching of the broad ligaments from repeated pregnancies results in the uterus tilting caudally and ventrally in the abdomen. This tilting likely impedes free flow of fluids from the uterine lumen thorough the cervix.

As the condition worsens, mares may develop lymphangiectasia. Uterine lymphatics return interstitial fluid and protein to the systemic circulation. During estrus, the uterine wall normally becomes edematous under the influence of estrogen. The interstitial fluid is reabsorbed by lymphatics as estrogen begins its decrease 12 to 24 hours before ovulation. Mares that are identified as having delayed uterine clearance and lymphangiectasia accumulate a black tarry fluid in the uterine lumen and have severe, diffuse lymphocytic, plasmacytic endometritis in response to an intrauterine infusion of 40 ml of India ink during diestrus. In contrast, India ink is reabsorbed into the endometrium of reproductively normal mares and is found in the iliac and thoracic lymph nodes by 24 hours after its infusion. Lymphangiectasia may occur secondary to prolonged uterine inflammation or secondary to an-

Although biopsy can reveal the presence of an inflammatory condition, other methods (such as examination of perineal conformation) must be employed to reveal why the condition is present, and a culture is needed to identify the particular pathogen. A repeat biopsy after appropriate therapy may reveal the degree of success of treatment.

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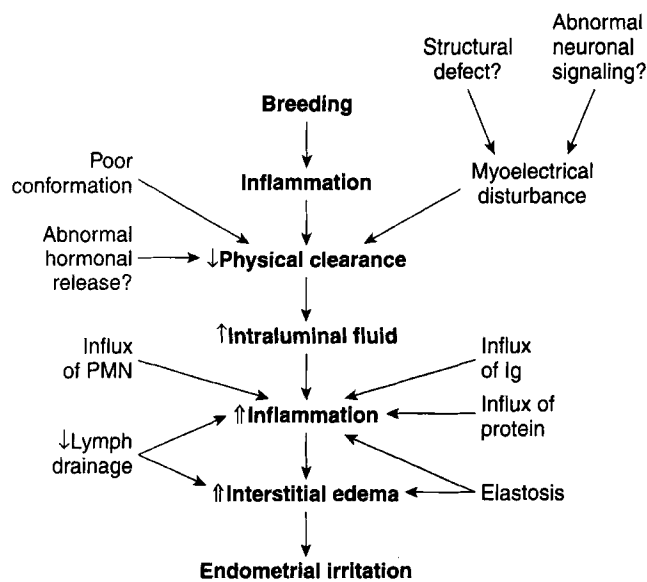
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rial inoculation or after breeding. Mares with delayed uterine clearance exhibit a decrease in the intensity and the duration of uterine contractions and have a delayed response to uterine infection in comparison to fertile mares. The cause of the defect is not known.

Other factors that contribute to a mare's inability to clear the uterus include increasing age and parity that coincides with a lengthening of the vulva and cranial tilting of the vulva. The changes are likely a consequence of repeated pregnancies, loss of body condition, and genetics. Loss of the structural support of the caudal reproductive tract and stretching of the broad ligaments from repeated pregnancies results in the uterus tilting caudally and ventrally in the abdomen. This tilting likely impedes free flow of fluids from the uterine lumen thorough the cervix.

As the condition worsens, mares may develop lymphangiectasia. Uterine lymphatics return interstitial fluid and protein to the systemic circulation. During estrus, the uterine wall normally becomes edematous under the influence of estrogen. The interstitial fluid is reabsorbed by lymphatics as estrogen begins its decrease 12 to 24 hours before ovulation. Mares that are identified as having delayed uterine clearance and lymphangiectasia accumulate a black tarry fluid in the uterine lumen and have severe, diffuse lymphocytic, plasmacytic endometritis in response to an intrauterine infusion of 40 ml of India ink during diestrus. In contrast, India ink is reabsorbed into the endometrium of reproductively normal mares and is found in the iliac and thoracic lymph nodes by 24 hours after its infusion. Lymphangiectasia may occur secondary to prolonged uterine inflammation or secondary to an-



**Figure 5.5-1** Pathogenesis of persistent mating-induced endometritis. *Ig*, Immunoglobulin; *PMN*, polymorphonuclear leukocyte.

giosis. Angiosis is a degeneration of the arteriole walls identified histologically as an increase in elastin deposition around uterine vessels. It is directly correlated to parity. It is hypothesized that elastosis results from repeated stretching of the uterine arterioles from numerous pregnancies and is associated with excessive uterine edema.

The theory that describes the pathogenesis of delayed uterine clearance—called *persistent mating-induced endometritis*—is presented in Figure 5.5-1. Transient inflammation is a normal physiologic response to mating. It removes excess spermatozoa, seminal plasma, and contaminants before the embryo enters the uterus. Normal mares clear the inflammation within 36 hours; however, neutrophil numbers are highest in the uterine lumen between 8 and 12 hours after breeding. Mares that fail to clear the semen-induced inflammation within 36 hours accumulate fluid in the uterine lumen. This fluid contains neutrophils, immunoglobulins, protein, semen, bacteria and other byproducts of inflammation. Retention of fluid results in prolonged interstitial edema. The endometrial mucociliary barrier may be damaged if fluid persists in the uterine lumen for a prolonged time. Lymphangiectasia and angiopathies contribute to the interstitial edema, as the lymphatics cannot drain the excessive edema and the latter leaks fluid into uterine tissues. The longer the process continues, the more likely that the endometrial barrier that prevents bacterial colonization will be damaged. The end result is an inhospitable environment for the embryo when it descends into the uterus and in some cases an ensuing bacterial endometritis.

## HISTORY AND CLINICAL SIGNS

The mare's reproductive history often provides the strongest evidence that she may be experiencing persistent mating-induced endometritis because clinical findings vary considerably with the time of year that the reproductive examination is performed. A typical history of

an affected mare is that she is pluriparous, greater than 14 years of age, and has poor perineal conformation. Historically, the mare conceives without difficulty for three to four pregnancies and then begins to experience bouts of infertility. She may have difficulty conceiving when she has the fourth foal by her side but conceives on the first mating during the subsequent spring. The mare delivers her fifth foal without difficulty early in the season but does not conceive after repeated breeding attempts that year. As these mares age, the degenerative changes within their uterus increase, and uterotonic drugs are less effective in removing intrauterine fluid. These mares will likely develop chronic infectious endometritis and will have only a fair to poor chance of carrying a foal until term.

Maiden mares, regardless of age, may also develop persistent mating-induced endometritis because their cervix does not relax sufficiently during estrus to allow drainage of uterine fluids. This condition occurs most commonly in aged performance mares that are first bred when they are in their teens, but it may be seen in young, nervous mares. The typical history is that the mare had a successful performance career, was retired at 12 to 14 years of age, and now has difficulty conceiving. The cause for the cervical malfunction is not known. The problem appears to resolve once the mare delivers her first foal.

## DIAGNOSIS

A definitive diagnosis can be made 12 to 36 hours after breeding. Mares with the condition will have intrauterine fluid visible by ultrasonography. However, treatment needs to be conducted before this time to obtain the highest pregnancy rates. A presumptive diagnosis can be made from the mare's past reproductive history. Mares that are suspected of having the condition should have a complete breeding soundness examination performed. The examination should include a physical, a body condition score, identification of previous or existing foot problems, and examination of the mare's perineal conformation. The length and slope of the croup and vulvar lips should be evaluated. Anatomic defects that predispose the mare to pneumovagina or vestibulovaginal reflux should be corrected surgically. The reproductive examination should include rectal palpation of the tract, ultrasonography, vaginal speculum examination, digital examination of the cervix, cytology and bacterial culture of the uterus, and in some cases a uterine biopsy or endoscopy of the uterus.

Findings on reproductive examination may differ by the time of year of the examination and the proximity of the examination to the last insemination. Most mares susceptible to persistent mating-induced endometritis exhibit minimal signs of inflammation before the first breeding of the year most likely because they have had prolonged sexual rest. Bacteria are not commonly isolated from uterine swabs, nor are neutrophils recovered from cytologic specimens. Endometrial biopsy score may be a Category IIA (using the Kenney grading system, 1978) with mild, focal inflammation with or without lymphangiectasia seen histologically. Periglandular fibrosis is frequently mild. However, after repeated breedings, fluid may be observed in the uterine lumen during estrus before breeding; the vagina may be inflamed; or a vaginal discharge may be

present. Some mares are identified at the first pregnancy examination conducted 14 to 16 days after ovulation because intrauterine fluid may be observed ultrasonographically. It is at these latter examinations that bacteria may be isolated, and cytologic specimens obtained from the uterus are frequently positive for neutrophils. An endometrial biopsy taken from this latter group of mares may be categorized as II or IIB, with the primary lesions of diffuse, moderate neutrophilic, lymphocytic inflammation combined with lymphangiectasia. By definition, if bacteria are recovered from the uterus of a mare exhibiting infertility the diagnosis is chronic, infectious endometritis. However, the underlying problem often is persistent mating-induced endometritis that was not managed properly at the time of breeding or has worsened in severity such that treatment is not effective.

## TREATMENT

The longer seminal byproducts remain in the uterine lumen, the greater the inflammatory response and the higher the likelihood of endometrial damage. Therefore treatment of mares susceptible to persistent mating-induced endometritis is directed at rapid removal of fluids. This can be accomplished by performing a uterine lavage to remove pus and debris, followed by administration of a uterotonic drug. This author advises that the uterus is lavaged between 4 and 8 hours after breeding and the mare is given 10 to 20 IU of intravenous oxytocin. The uterus can be flushed with warm saline, with lactated Ringer's, or with a balanced salt solution. This author prefers to use a Bivona catheter (Bivona, Inc., Gary, Ind.) attached to tubing that fits into a 1 liter flask. One liter of solution is placed into the uterus by gravity flow and is collected into a flask on the ground. The procedure is repeated three times. The clarity of the efflux is evaluated. It is normal for the first liter of efflux to be cloudy 4 to 8 hours after breeding as pus is from the physiologically inflammatory response directed against the semen. The second and third liters of efflux should be clear. Cloudy efflux collected in the second or third liter indicates that the inflammatory response is significant and that it may be prolonged. Mares that have 2 to 3 liters of cloudy efflux recovered from their uterus need to be reevaluated at 24 hours after breeding. The majority of these mares will have fluid in their uterus at 24-hour examination and will require a second uterine lavage and a second treatment with oxytocin. This author suggests that all mares with persistent mating-induced endometritis be evaluated 24 hours after breeding. Those mares with intrauterine fluid should be treated a second time with uterine lavage and oxytocin. Some veterinarians will treat all suspect mares with oxytocin at 24 hours after breeding; however, no data support or refute the repeated treatment.

The rationale for lavage of the uterus at 4 to 8 hours after breeding is to delay treatment long enough to ensure that viable sperm are not prematurely washed out of the uterus and to perform it soon enough that inflammatory byproducts do not remain in prolonged contact with the endometrium. Pregnancy rates are decreased if the uterus is flushed or if oxytocin is given within 2 hours of breeding. Eight hours was chosen as the upper limit because the

normal physiologic inflammatory response to semen is greatest between 8 and 12 hours after breeding in reproductively normal mares. In addition, when mares susceptible to endometritis receive an inoculum of *Streptococcus equi* subspecies *zooepidemicus*, the bacteria proliferate and grow exponentially in the uterus for the first 5 hours. Their numbers decrease to undetectable levels by 9 hours and then begin to increase exponentially. No bacteria are recovered from reproductively normal mares later than 9 hours postinoculation. Therefore 8 to 12 hours after mating appears to be the critical time by which uterine debris is cleared in reproductively normal mares. Recent work from Europe shows that twice as many mares with persistent mating-induced endometritis that received a uterine lavage between 4 and 6 hours after insemination (6 of 9) were pregnant than mares that received a lavage 18 to 20 hours after insemination (3 of 9). Treatment needs to be performed after each breeding, as it is the semen that causes the physiologic inflammation.

Mares that have persistent mating-induced endometritis and lymphangiectasia can be treated with a combination of uterine lavage (3 L) and oxytocin (10-20 IU) at 4 to 8 hours after breeding and cloprostenol (250 micrograms; Estrumate) at 12 and 24 hours after breeding. The rationale for the combined therapy is that oxytocin induces strong uterine contractions for 30 to 50 minutes, thereby assisting in the clearance of fluids that have accumulated within the uterine lumen. Cloprostenol induces lower amplitude contractions than oxytocin; however, the contractions persist for 4 to 5 hours. As no smooth muscle exists within the lymphatics, pressure exerted by muscle on the lymphatics stimulates flow of lymph. Cloprostenol appears to assist in the removal of interstitial edema because of its ability to produce sustained, low-grade myometrial contractions. However, it needs to be used with caution. If it is administered after ovulation, it can interfere with the production of progesterone by the corpus luteum. Pregnancy rates are decreased if cloprostenol is administered 48 hours after ovulation. This author has limited its use to 12 and 24 hours after breeding and does not advocate its use in mares bred with frozen semen after ovulation.

The use of intrauterine antibiotics in mares with persistent mating-induced endometritis that have no bacteria isolated from their uterus is controversial. Experimental data indicate that antibiotics may not be needed, even in cases of bacterial contamination if mares are treated with uterine lavage or uterotonic drugs within 12 hours of mating. Clinical data have shown that pregnancy rates can be increased in a large group of mares if intrauterine antibiotics are combined with oxytocin; however, uterine lavage was not performed consistently in all mares within 12 hours of breeding. It is difficult in field situations to always lavage mares within the 4- to 8-hour time frame, but it should be attempted because data show that this treatment is associated with the highest pregnancy rates. This author does not advocate the use of intrauterine antibiotics in mares if no bacteria have been isolated from their uterus. If bacteria are isolated, the mare should be treated with intrauterine antibiotics for a minimum of 4 to 5 days during the estrus in which the bacteria were isolated. It is not advisable to breed the mare on that cycle, as concep-



tion rates are lower and early embryonic death rates are higher.

Mares susceptible to persistent mating-induced endometritis should be bred no more than once per cycle—within 48 hours of ovulation if bred by natural cover and within 24 hours if bred with cooled semen. It is recommended that these mares not be bred with frozen semen, as the subsequent physiologic inflammation may be more severe because of the lack of seminal fluid in the processed semen. In addition, pregnancy rates tend to be lower with frozen semen than when mares are bred with either fresh or cooled semen. Treatments after breeding need to be timed with breeding and not with ovulation. This author suggests that mares receive one to two uterine lavages, with the first conducted between 4 and 8 hours after breeding and the second at 24 hours after breeding. The number of times one enters the uterus with one's hand should be limited after breeding and especially after ovulation because bacteria may be instilled into the uterus iatrogenically. The vestibule contains a large and a varied amount of pathogenic bacteria that can be easily carried cranially into the uterus with one's hand. The dose and

frequency of oxytocin should be limited to 10 to 20 IU given at least 4 hours apart. Larger doses of oxytocin have been associated with a decrease in pregnancy rate, possibly because it induces a tetanic contraction and not a propagating contraction. If given more frequently than every 4 hours, uterine contractions are weaker, most likely because oxytocin receptors in the endometrium are down-regulated. No data indicate that increasing the dose of oxytocin or giving it repeatedly after breeding improve pregnancy rates.

### Supplemental Readings

Knutti B, Pycock JF, van der Weijden GC et al: The influence of early postbreeding uterine lavage on pregnancy rate in mares with intrauterine fluid accumulations after breeding. *Equine Vet Educ* 2000; 2:346-349.

Troedsson MHT, Ababneh MM, Ohlgren AF et al: Effect of peri-ovulatory prostaglandin  $F_{2\alpha}$  on pregnancy rates and luteal function in the mare. *Theriogenology* 2001; 55:1891-1900.

## CHAPTER 5.6

# Photoperiod Manipulation

DAN C. SHARP  
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In many breed types, the greater economic value of early-born foals has made early induction of estrus cyclicity in mares the "Holy Grail" of reproductive management. Springtime (vernal) transition from anestrus into the breeding season, marked by the first ovulation of the year, does not take place until the first week of April, essentially without regard for location within the temperate zone. The vernal transition period preceding first ovulation is marked by ambiguous signs, such as prolonged estrous behavior and development of large but anovulatory follicles and can be a confusing and frustrating time for breeders and veterinarians alike. The current state of knowledge suggests that events of the vernal transition are very difficult to override, which means that the best methods for accelerating the time of first ovulation of the year involve accelerating the entire process. In these authors' opinion, no treatment has yet successfully truncated or bypassed the vernal transition. Rather, the most successful methods take advantage of the naturally occurring events and attempt to accelerate their progress or hasten their initiation. Table 5.6-1 lists the events of vernal transition in chronologic order.

The most successful method of managing early breeding in mares is use of artificial photoperiod. Artificially lengthening the day, first reported in the 1940s in England, starts the process of transition earlier than when mares exist in natural light alone. The key phrase here is "start the process of transition earlier," as exposure to artificial light does not seem to truncate or by-pass the transition phase; it merely begins it sooner. Therefore beginning a program of artificial light stimulation early enough to enjoy the benefits is important. For instance, if a breeder wants to get mares bred by the end of February and the transition period requires a minimum of 6 to 8 weeks, light exposure must begin by mid-December. These authors have always had useful results when light exposure starts by late November. One reason for starting early is to observe a given mare for one or more cycles before breeding.

Considering that fact, the particular program for exposing mares to artificial light appears to have a great deal of latitude. Four general types of lighting programs have been published, each with sufficient success to be considered, depending on the individual farm's management and facilities (Table 5.6-2).

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Considering that fact, the particular program for exposing mares to artificial light appears to have a great deal of latitude. Four general types of lighting programs have been published, each with sufficient success to be considered, depending on the individual farm's management and facilities (Table 5.6-2).

**Table 5.6-1**  
**Physiologic Events of Vernal Transition in Chronologic Order**

Event	Approximate Time of Year	Impact	Change
Increased GnRH	Just after winter solstice (or within 2 weeks after photostimulation)	Stimulates FSH in pituitary (gene for LH production is turned off)	Anestrus characterized by extremely low GnRH, FSH, and LH
Increased circulating FSH	Detectable by second or third week of January in ponies	Stimulates ovarian follicles	FSH is low during anestrus
Increased follicular development	Detectable by early February in ponies	Large (>30 mm) follicles, but first 2 or 3 are anovulatory	Ovaries show no follicles >10 mm during anestrus
Mares exhibit 2 to 3 large nonovulating follicles	Throughout vernal transition; interval between successive follicles is 9 to 12 days	Increased follicular activity can be deceiving—especially if not monitored frequently	Little endocrine activity; follicles produce very little steroid hormone
Mares exhibit estrus	Throughout vernal transition; varies from sporadic to continuous	Mares often sent to stud inappropriately	Mares likely to be indifferent to stallion during anestrus
Follicles begin to secrete hormones	5 to 7 days before first ovulation of the year	Diagnostic potential and may stimulate LH	First significant increase in steroid hormones
Increase in LH secretion	5 to 7 days before first ovulation of the year	Renewal of LH gene; stimulates ovulation	Vernal transition ends and breeding season begins

*GnRH*, Gonadotropin-releasing hormone; *LH*, luteinizing hormone; *FSH*, follicle-stimulating hormone.

**Table 5.6-2**  
**Examples of Different Strategies for Stimulating Renewed Reproductive Activity in Anestrous Mares Using Artificial Lighting**

Type of Light Program	Method
Lights “instant on”	Usually individually lighted stalls with timers; 16 hours of light
Lights on gradually	Individually lighted stalls; duration of light exposure increased at same rate as in springtime, but begun in fall
Evening lights only	3 hours of light timed to come on at sunset; works well in a paddock area because mares can be turned out after just a few hours of light exposure
“Night interruption”	1 hour of light timed 9.5 hours after beginning of darkness; this system may not lend itself to paddock or other outdoor lighting programs

The question of how much light is enough is a common question for which no ready answer exists. Many anecdotal comments have been suggested, such as “enough light to read a newspaper” or “a 100-watt bulb for a 12' × 12' stall.” Clearly a more scientific approach would be beneficial, but few attempts to learn the minimum light threshold for triggering the renewal of reproductive activity have been made. However, most scientific experiments have used light

intensity in the region of 8 to 12 Foot candles (fc) of light—an amount that appears to be sufficient. For further comparison, Foot candles can be converted to Lux by multiplying by 10.76391; thus the lighting intensity commonly employed in scientific investigations of photoperiod in horses of 10 fc would be approximately 107.6391 lx. Although this may exceed the required light threshold, light of that intensity appears to be practical and successful.

Unfortunately, no formula for calculating expected illumination of every square foot of a stall or paddock is readily available. The reader is urged to consult with local lighting specialists before constructing a facility, especially an outdoor paddock which may require locating large light fixtures at sufficient height to provide ample coverage. A few guiding comments, however, can be helpful. First, remember that light intensity varies with the square of the distance from light source to object of interest. Thus although the human eye can perceive light emanating from its source, the actual *illuminance* or luminous flux that is received by an area diminishes with the square of the distance. The *luminous flux* is the light bathing an object or area some known distance from the light source and is measured as *lux* or  $\text{lm}/\text{m}^2$ . Although checking with local lighting experts is worthwhile, it is possible to do some seat-of-the-pants calculations as guidelines. For example, lighting fixtures recently installed at the University of Florida Horse Research Center were rated at 50,000 lumens at 464 watts. These fixtures, mounted on poles at a height of 15 feet, would be expected to produce a luminous flux of approximately  $20 \text{ lm}/\text{m}^2$ , each at 50 feet from the pole. Of course, there is more than one fixture, and their luminous fluxes overlap, thus creating a light intensity that has worked well. Some examples of typical illuminance situations are presented in Table 5.6-3.

**Table 5.6-3**  
**Examples of Typical Illuminance**

Typical Situation	Illuminance
Full sunlight	100,000 lx
Overcast day	10,000 lx
Office lighting	500 lx
Corridor lighting	100 lx
Light at dusk	50 lx
Moonlight (full)	0.5 lx
Starlight	0.2 lx

Another aid in setting up a successful lighting program is measuring the actual illuminance produced by a given facility. Once a facility is in place, the illuminance can be checked with a sophisticated light meter. Better yet, a through-the-lens metered, single lens reflex camera can be used to monitor light level. These authors recommend placing a plain white Styrofoam cup over the lens to act as a diffuser. With that in place, the shutter speed should be set to  $\frac{1}{4}$  sec and the ISO (ASA) to 400. With these settings, the meter can be read while the veterinarian walks around the stall or paddock. An f-stop reading of 4.0 or better (higher number) means that light intensity is probably sufficient to stimulate early onset of reproductive activity in anestrus mares.

The foregoing lighting programs have all been shown to be effective in stimulating early onset of the breeding season in mares, but it must be emphasized that these systems only begin the process earlier. Photoperiod stimulation has not been shown to truncate or shorten the process of vernal transition, and breeders can still expect development and subsequent regression of several (two to three) large anovulatory follicles before observing the first ovulation of the year.

One final caveat about the use of artificial lighting deserves mention. Although artificial lighting appears to be the most successful method for initiating renewal of reproduction in seasonal animals in general—and mares specifically—little information about the possible deleterious effects of repeatedly stimulating early onset of the breeding season is available. Importantly, it has been shown that continuous lighting (24 hr/day) can disrupt reproduction. The possibility that repeated stimulation of a mare's reproductive cycle with artificial light could lead to unwanted responses—such as refractoriness to stimulation or phase shifting of the annual rhythm—remain to be researched. Perhaps this issue is similar to the concerns about transporting stallions between hemispheres for continuous breeding. Such “shuttling” is tantamount to maintaining stallions in a stimulatory photoperiod, and the consequences, if any, are unknown.

## PHARMACOLOGIC INDUCTION OF ESTRUS

It is clear that use of artificial lighting is the most successful and most widely employed method for jump-starting the breeding season. However, is there hope for a phar-

macologic approach that does not require rewiring the farm? The short answer is that there is hope—but not necessarily promise.

Careful study of Table 5.6-1 reveals the problem to be surmounted in order for a mare to reinitiate estrous cyclicity. Luteinizing hormone (LH) secretion from the pituitary is, for all practical purposes, limiting throughout anestrus and vernal transition. These authors have shown that the gene for production of the LH subunits is not detectable in the pituitaries of anestrus mares. It is this reduction or outright lack of LH that appears to be responsible for the anovulatory vernal transition follicles. The reduction in pituitary LH appears to continue even after hypothalamic gonadotropin-releasing hormone (GnRH) secretion is renewed. That may explain the mixed results when GnRH is administered to mares in vernal transition in attempts to stimulate ovulation. Studies that employed this strategy several years ago were promising, but positive results likely reflected treatment given to mares further along in vernal transition. Similarly, studies using synthetic progestins to “stimulate” early onset of estrous cyclicity may have employed mares further along in vernal transition.

## Dopamine Antagonist and Seasonality in Horses

In species such as sheep, evidence indicates that dopamine plays an inhibitory role on the hypothalamic-pituitary axis (HPA) during the nonbreeding season. Specifically, gonadotropin secretion decreases during the nonbreeding season because of a neuronal inhibition of GnRH secretion via dopaminergic input. The inhibition of the HPA occurs only during anestrus and is estrogen-dependent.

Although a direct relationship between dopamine secretion and suppression of the equine HPA has not been demonstrated to date, dopamine concentrations in cerebrospinal fluid are highest in mares during anestrus. Thus recent interest in studying the effects of various dopamine antagonists on the equine hypothalamic-pituitary-gonadal axis and their subsequent effects on the timing of the breeding season in mares has been considerable.

The first dopamine antagonist to be tested was sulpiride at a dose of 0.5 mg/kg, orally every 12 hours. This dose caused a significant advance of the onset of the breeding season. Similarly, when domperidone (1.1 mg/kg once daily orally), another dopamine antagonist, was administered to horses during early vernal transition, it resulted in a significant advance of the onset of the breeding season over that in control mares. The primary difference between sulpiride and domperidone is that sulpiride crosses the blood-brain barrier, whereas domperidone does not.

The reported effect of dopamine antagonist on accelerating the onset of the breeding season in mares has been further evaluated to determine what effect, if any, the antagonist has on the hypothalamic-pituitary axis. Brendemuehl and Cross (2000) treated anestrus mares with domperidone beginning on January 15 and reported no effect on FSH, LH, nor estradiol secretion. However, Brendemuehl and Cross (see readings list) reported a significant advance in the onset of the breeding season in those mares treated with domperidone (51 days versus 130 days). Similarly, unpublished data from laboratory of the

authors of this chapter reported that anestrus pony mares treated with sulpiride twice daily for 2 weeks during winter anestrus were not different from control mares with respect to LH and GnRH secretion. Therefore the data suggest that dopamine antagonist may accelerate the onset of the breeding season in vernal transition mares but not through activation of the hypothalamic-pituitary axis. Recent work by Daels and colleagues (2000; see readings list) reported that treatment of anestrus mares with daily sulpiride plus extended photoperiod and ambient temperature resulted in an advance of the onset of the breeding season. However, when mares were treated with sulpiride alone and maintained under natural photoperiod and natural temperatures, no difference in date of the first ovulation of the year was found. It is important to note that no data on the fertility of the reported "early" ovulations exist.

Although the current evidence that suggests that dopamine antagonist may be helpful in manipulating the timing of the first ovulation of the year in mares is promising, variation in results may again suggest that treatment

efficacy depends to some extent on the photic status of the mare. As in many experimental treatments, timing of treatment may be critical relative to photic exposure (anestrus versus vernal transition). These authors have proposed the idea of a "photic gate," which means that some neural mechanism(s) require exposure to stimulatory photoperiods before pharmacologic initiation of estrous cyclicity can be accomplished.

### Supplemental Readings

- Brendemuehl JP, Cross DL: Influence of the dopamine antagonist domperidone on the vernal transition in seasonally anoestrous mares. *J Reprod Fertil* 2000; 56(Suppl):185-193.
- Daels PF, Fatone S, Hansen BS et al: Dopamine antagonist-induced reproductive function in anoestrous mares: gonadotropin secretion and the effects of environmental cues. *J Reprod Fertil* 2000; 56(Suppl):173-183.
- Reiter RJ: The melatonin rhythm: both a clock and a calendar [review]. *Experientia* 1993; 49(8):654-664.

## CHAPTER 5.7

# Induction of Ovulation

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**H**ormonal induction of ovulation is a common breeding management practice in the equine industry. Ovulation induction is routinely performed if the stallion is in high demand, if semen is limited, or if a single insemination is desired (i.e., for mares with a severe persistent postmating inflammatory response). Induction of a timed ovulation may also be beneficial in mares bred with frozen or cooled-transported semen, for mares at the end of the spring transition period, and for synchronization of ovulation. Stimulation of ovulation may not be needed if the stallion is at the same facility as the mare, if semen is not limited, or in pasture breeding programs. Hormones routinely used to induce ovulation in mares include human chorionic gonadotropin (hCG) and gonadotropin-releasing hormone (GnRH) agonists. Alternative agents for ovulation management have been investigated, but most have limited efficacy (i.e., prostaglandins) or limited availability (i.e., partially purified equine luteinizing hormone).

### HUMAN CHORIONIC GONADOTROPIN

Human chorionic gonadotropin is a large glycoprotein hormone produced by cytotrophoblasts of the human pla-

centa. The hormone has luteinizing hormone (LH) biologic activity when administered to horses and other species. Administration of hCG to mares in behavioral estrus, with mild to moderate uterine edema and a follicle greater than or equal to 35 mm in diameter will usually induce ovulation in approximately 36 hours. Dosages used to induce ovulation range from 1000 to 3300 IU. The hCG product (Chorulon, Intervet Inc., Millsboro, Del.) commonly used in equine ovulation management is not specifically approved for use in horses.

Human chorionic gonadotropin is very effective in inducing ovulation in mares that have not received the hormone previously and in mares receiving the hormone for the first time in a breeding season. Efficacy may be markedly reduced when hCG is used on an individual mare repeatedly during a single breeding season. The cause of the reduced efficacy after repeated use is presumed to be development of anti-hCG antibodies. Although some studies have reported that use of hCG multiple times during a breeding season results in decreased efficacy in inducing a timed ovulation, other studies have suggested that the presence of high antibody titers is not associated with a loss of efficacy.

In general, hCG use should be limited to one or two estrous cycles during a breeding season. If inductions of ad-

authors of this chapter reported that anestrus pony mares treated with sulpiride twice daily for 2 weeks during winter anestrus were not different from control mares with respect to LH and GnRH secretion. Therefore the data suggest that dopamine antagonist may accelerate the onset of the breeding season in vernal transition mares but not through activation of the hypothalamic-pituitary axis. Recent work by Daels and colleagues (2000; see readings list) reported that treatment of anestrus mares with daily sulpiride plus extended photoperiod and ambient temperature resulted in an advance of the onset of the breeding season. However, when mares were treated with sulpiride alone and maintained under natural photoperiod and natural temperatures, no difference in date of the first ovulation of the year was found. It is important to note that no data on the fertility of the reported "early" ovulations exist.

Although the current evidence that suggests that dopamine antagonist may be helpful in manipulating the timing of the first ovulation of the year in mares is promising, variation in results may again suggest that treatment

efficacy depends to some extent on the photic status of the mare. As in many experimental treatments, timing of treatment may be critical relative to photic exposure (anestrus versus vernal transition). These authors have proposed the idea of a "photic gate," which means that some neural mechanism(s) require exposure to stimulatory photoperiods before pharmacologic initiation of estrous cyclicity can be accomplished.

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## CHAPTER 5.7

# Induction of Ovulation

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**H**ormonal induction of ovulation is a common breeding management practice in the equine industry. Ovulation induction is routinely performed if the stallion is in high demand, if semen is limited, or if a single insemination is desired (i.e., for mares with a severe persistent postmating inflammatory response). Induction of a timed ovulation may also be beneficial in mares bred with frozen or cooled-transported semen, for mares at the end of the spring transition period, and for synchronization of ovulation. Stimulation of ovulation may not be needed if the stallion is at the same facility as the mare, if semen is not limited, or in pasture breeding programs. Hormones routinely used to induce ovulation in mares include human chorionic gonadotropin (hCG) and gonadotropin-releasing hormone (GnRH) agonists. Alternative agents for ovulation management have been investigated, but most have limited efficacy (i.e., prostaglandins) or limited availability (i.e., partially purified equine luteinizing hormone).

### HUMAN CHORIONIC GONADOTROPIN

Human chorionic gonadotropin is a large glycoprotein hormone produced by cytotrophoblasts of the human pla-

centa. The hormone has luteinizing hormone (LH) biologic activity when administered to horses and other species. Administration of hCG to mares in behavioral estrus, with mild to moderate uterine edema and a follicle greater than or equal to 35 mm in diameter will usually induce ovulation in approximately 36 hours. Dosages used to induce ovulation range from 1000 to 3300 IU. The hCG product (Chorulon, Intervet Inc., Millsboro, Del.) commonly used in equine ovulation management is not specifically approved for use in horses.

Human chorionic gonadotropin is very effective in inducing ovulation in mares that have not received the hormone previously and in mares receiving the hormone for the first time in a breeding season. Efficacy may be markedly reduced when hCG is used on an individual mare repeatedly during a single breeding season. The cause of the reduced efficacy after repeated use is presumed to be development of anti-hCG antibodies. Although some studies have reported that use of hCG multiple times during a breeding season results in decreased efficacy in inducing a timed ovulation, other studies have suggested that the presence of high antibody titers is not associated with a loss of efficacy.

In general, hCG use should be limited to one or two estrous cycles during a breeding season. If inductions of ad-

ditional timed ovulations are desired, use of an alternative such as the GnRH agonist deslorelin acetate should be considered.

## GONADOTROPIN-RELEASING HORMONE

Deslorelin acetate (Ovulent, Fort Dodge Animal Health, Fort Dodge, Iowa) is a potent gonadotropin-releasing hormone agonist approved for use in the United States for the induction of ovulation in mares. The commercial product consists of a biocompatible implant that contains 2.1 mg of deslorelin. The GnRH agonist stimulates release of LH from the anterior pituitary, which induces follicle maturation and ovulation. Deslorelin has been reported to be very effective in inducing ovulation when administered to a mare in estrus with a follicle greater than or equal to 35 mm in diameter. Approximately 84% of mares treated with deslorelin ovulate within 48 hours, and 93% ovulate within 72 hours after treatment. Repeated use during a breeding season does not result in antibody formation or a decrease in efficacy.

Several studies have reported that the interovulatory interval may be prolonged in mares induced to ovulate with deslorelin that do not become pregnant. Administration of the implant has been reported to cause a prolonged suppression (down-regulation) of follicle-stimulating hormone (FSH) release and a decrease in follicular development in the diestrous period following the induced ovulation. The overall result may be a slight to markedly prolonged interovulatory interval. Administration of prostaglandins to lyse the corpus luteum formed after a deslorelin-induced ovulation exacerbates the adverse effects on pituitary and ovarian function. However, removal of the deslorelin implant 48 hours after administration prevents the adverse effects on FSH secretion and follicular development and does not alter ovulation rates. Consequently, it is recommended that

to decrease the potential for a prolonged interovulatory interval in mares that do not become pregnant the deslorelin implant be removed approximately 48 hours after administration or at the time ovulation is detected. For ease of removal, the implant may be inserted subcutaneously by using the implant device provided by the manufacturer in a region of the vulva that has been infused with 1 ml of lidocaine. After ovulation, the implant may be removed through the original tract created by the implant device by using gentle topical pressure. No subsequent treatment is required at the site after implant removal.

## USE OF HUMAN CHORIONIC GONADOTROPIN OR GONADOTROPIN-RELEASING HORMONE IN A COOLED-TRANSPORTED SEMEN PROGRAM

The goal of most transported semen programs is to ship semen one time for each mare during a given estrous cycle. Closely monitoring the reproductive cycle of the mare to predict and detect ovulation is therefore desirable. In addition, hCG or GnRH are commonly used to induce a predictable timed ovulation. Ovulation-inducing hormones may be administered at the time semen is ordered or when the semen shipment arrives at the farm. Administration of hCG or GnRH when the semen is ordered results in a decreased time interval from insemination to ovulation. This strategy may be particularly advantageous if longevity of the spermatozoa is limited. However, if hCG or GnRH is administered at the time semen is ordered and the stallion subsequently cannot be collected or semen does not arrive at the scheduled time, ovulation may occur before the mare is inseminated. Treatment with hCG or GnRH after the semen arrives will avoid these potential complications and will still promote ovulation within 48 hours after insemination.

### BOX 5.7-1

#### Insemination Protocols for Mares Induced to Ovulate with Human Chorionic Gonadotropin or Gonadotropin-Releasing Hormone and Bred with Frozen Semen

##### Human Chorionic Gonadotropin

1. Administer hCG (2500 IU IV) at 4:00 PM if the mare is in estrus, has uterine edema, and a follicle greater than or equal to 35 mm in diameter is present.
2. Perform ultrasound on mare the next morning (8:00 AM). Inseminate the mare only if a fresh ovulation is detected.
3. Perform ultrasound and inseminate with frozen semen at 4:00 to 6:00 PM (24-26 hr after hCG was administered).
4. Perform ultrasound on mare at 8:00 AM the following day (40 hr after hCG administration); inseminate again if mare has ovulated; if mare has not ovulated, recheck at 6- to 8-hour intervals and inseminate when ovulation is detected.

##### Gonadotropin Releasing Hormone (GnRH)

1. Administer GnRH (2.1 mg SQ) at 8:00 AM if the mare is in estrus, has uterine edema, and a follicle greater than or equal to 35 mm in diameter is present.
2. Perform ultrasound on mare the next morning (8:00 AM). Inseminate the mare only if a fresh ovulation is detected.
3. Perform ultrasound and inseminate with frozen semen at 4:00 to 6:00 PM (32-34 hr after GnRH was administered).
4. Perform ultrasound on mare at 8:00 AM the following day (48 hr after GnRH administration); inseminate again if mare has ovulated; if mare has not ovulated, recheck at 6- to 8-hour intervals and inseminate when ovulation is detected.

hCG, Human chorionic gonadotropin; GnRH, gonadotropin-releasing hormone; SQ, subcutaneous.

### USE OF HUMAN CHORIONIC GONADOTROPIN OR GONADOTROPIN-RELEASING HORMONE IN A FROZEN SEMEN PROGRAM

The use of frozen semen requires intensive reproductive management of the mare. Insemination of frozen-thawed semen within 12 hours before ovulation and/or within 6 to 8 hours after ovulation is recommended. Subsequently, mares are routinely examined by palpation and ultrasonography every 6 to 8 hours once a large pre-ovulatory follicle is detected. Administration of hCG or GnRH to mares being bred with frozen semen may significantly decrease the number of examinations required to predict and detect ovulation. Protocols for the use of hCG and GnRH in a frozen semen breeding program are presented in Box 5.7-1. A majority of mares may be inseminated with frozen semen within 12 hours before ovulation and again within 6 hours after ovulation by using these protocols.

In summary, induction of a predictable timed ovulation can be successfully accomplished in estrual mares with follicles greater than or equal to 35 mm by using either hCG or GnRH. It is recommended that hCG be used

only once or twice per season in a given mare and that GnRH be used in subsequent cycles or in mares in which hCG has not been effective. Furthermore, removal of the GnRH implant 48 hours after administration is advised to prevent the possibility of a prolonged interovulatory interval if the mare does not become pregnant.

#### *Supplemental Readings*

- Farquhar VJ, McCue PM, Nett TM et al: Effect of deslorelin acetate on gonadotropin secretion and ovarian follicle development in cycling mares. *J Am Vet Med Assoc* 2001; 218:749-752.
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## CHAPTER 5.8

# Use of Ultrasound to Stage Estrus and Predict Ovulation

JONATHAN F. PYCOCK  
*North Yorkshire, England*

Once the mare has entered the ovulatory season, the estrous cycle is on average 22 days long. The follicular phase—that is, the period from luteal regression to ovulation—typically lasts 5 to 7 days, and the luteal phase—the period from ovulation to luteal regression—lasts 14 to 16 days. Estrus is the period of acceptance of the stallion, which can end anything from 12 to 84 hours after ovulation. Diestrus is the term used to describe the whole period from ovulation until regression of the corpus luteum (CL). Estrus may include only part of the follicular phase and may persist into the early part of the luteal phase.

Cycle length varies enormously, particularly early in the breeding season when cycle length is longest. Late in the breeding season, cycle length is shortest. The wide variability between cycles is normally due to variation in the length of estrus rather than diestrus; estrus may last from 2 to 14 days. Ability to predict the timing of ovulation with accuracy may be necessary so that mares may

be mated within the best time relative to ovulation to achieve optimal pregnancy rates and to conserve the use of busy stallions. For pregnancy rates to be maximal, normal mares should be bred within 48 hours of ovulation. For mares bred artificially, insemination should be even closer to ovulation—within 24 hours for chilled semen and within 8 hours for frozen semen. A major part of the practitioner's work is the examination of mares to stage estrus and predict ovulation, and it is without doubt the most difficult. Parameters used to estimate the time of ovulation and thus the optimum time for breeding varies widely. Both the ovaries and the uterus need to be examined thoroughly at every examination of a mare. The introduction of transrectal ultrasound technology to image the reproductive tract in mares has allowed cyclic changes in the ultrasonic morphology of the reproductive tract to be studied. Ovarian features to note are follicle size, softness, and shape; echogenicity and thickness of the granulosa layer; and presence of small echogenic particles



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within the follicular fluid. The interpretation of endometrial ultrasonic morphology also forms an important part of establishing an accurate estimate of the stage of estrus.

### FOLLICULAR CHANGES

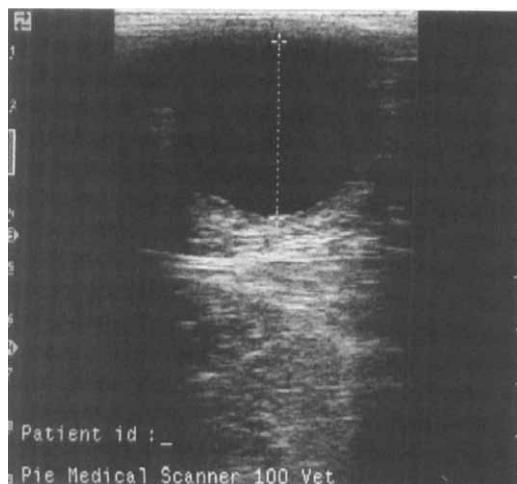
For accurate prediction of ovulation, the genital tract should be evaluated daily by both palpation and ultrasonography. Palpation remains a key component of the examination to identify all structures and provide information on their texture. The diameter and location of all follicles greater than 20 mm and all luteal structures should be noted. Detection of the CL with ultrasound is an important skill to acquire because follicle development in the mare can occur during diestrus, and detection of a large (>35 mm) follicle does not necessarily mean the mare is in estrus. When the follicle is associated with estrus, the cervix is relaxed; there is no functional CL detected on ultrasound examination; and in most cases a degree of uterine edema is present.

In many cases mares are presented for examination when they are on the first day of standing estrus. On ultrasonic evaluation it should be confirmed that no CL is present in the ovaries, and the size of any follicles greater than 20 mm should be noted. Follicles usually retain their spheric shape and have a circular image on ultrasound until they are over 40 mm in size and within 48 hours of ovulation. Accurate measurement of the follicle is important to monitor its growth. The largest visible diameter should be recorded and the electronic callipers on the ultrasound machine should be accurately placed and the measurement recorded (Figure 5.8-1). When measured accurately, diameter correlates well with volume—but only while the follicle is spheric. Ovulation usually occurs when the follicle approaches 40 mm or above and rarely occurs below 30 mm. Size of follicle at ovulation is often quoted as a reliable predictor of ovulation but is too variable between individual mares to be useful. Some mares will ovulate from small (<30 mm) follicles, whereas

other mares, especially draft breeds, do not ovulate until follicle size is 50 mm or more. Several factors influence follicle size at ovulation; breed and time of year are the two main factors. Thoroughbred and Standardbred mares ovulate from significantly smaller follicles than warmbloods and heavier draft-type horses. Mares tend to ovulate from larger follicles in early spring than midsummer. In addition, mares that develop twin follicles have a further reduced follicle diameter (about 5 mm) at ovulation.

Follicles measuring more than 25 mm grow at 3 to 4 mm/day, and as the follicle grows in size, it begins to soften. Distinct softening of the follicle does not usually occur until at least 48 hours before ovulation. The mare may become more sensitive to palpation of the ovary when ovulation is approaching. The feel of the follicle on palpation is a useful guide to its maturity, particularly with larger follicles. Follicles within 48 hours of ovulation are normally easily palpable and protrude from the ovarian surface and are at least “springy” rather than hard. This moderate softening can be misleading because the follicle may undergo some softening several days before ovulation, whereas other follicles do not soften at all. Very soft follicles are usually about to ovulate within a matter of hours. Follicular softening can be detected by ultrasound as well as palpation because an otherwise spheric (circular) follicle appears to be flattened at the surface in contact with the ultrasound transducer (Figure 5.8-2). As a follicle softens it becomes increasingly difficult to obtain a satisfactory image to measure the diameter without exerting enough pressure to deform the outline of the follicle.

Changes other than flattening may be observed in the follicle within 48 hours of ovulation. The most frequent changes are change of shape. The follicle becomes ovoid as ovulation approaches, and a small outpouching of the follicle points toward the ovulation fossa and thus results in a pear shape.



**Figure 5.8-1** An ultrasound image (5-MHz transducer, scale in cm) of a 3-cm follicle. Note callipers measuring the largest visible diameter.



**Figure 5.8-2** An ultrasound image (5-MHz transducer) of a large (4.2-cm) follicle. Note the flattening of the dorsal surface of the follicle and increased thickness and echogenicity of the follicular wall.

In the 48 hours—but more obviously in the 12- to 24-hour period—before ovulation, the wall of the follicle (granulosa layer) becomes increasingly echogenic and appears thickened. As ovulation approaches, the follicle wall may become intensely hyperechoic and irregular in outline. Immediately before follicular collapse, the follicle may appear “separated” into two or three compartments. Small echogenic particles may appear in the follicular fluid close to ovulation. These particles are thought to result from preovulatory hemorrhage. If the particles continue to increase in density and become widespread and if the follicle diameter increases in diameter to 50 or 60 mm (occasionally even more), these follicles rarely ovulate. An anechoic layer located beneath the follicle wall may be detectable. This anechoic layer becomes more prominent as ovulation approaches.

In this author's experience, none of these factors is consistently reliable enough for making practical estimates of the timing of ovulation. In some cases these features may appear days before ovulation or not at all. It is important to use all the parameters in combination, and serial examinations at 24- or 48-hour intervals are helpful in making this decision. The most constant factor in follicle size at ovulation is the individual mare. Knowledge of previous ovulatory diameter is especially valuable in mares that ovulate from unusually small or particularly large follicles. These mares will tend to do so consistently.

## UTERINE CHANGES

The ability to predict ovulation can be improved by using the pattern of endometrial edema. During diestrus, individual endometrial folds are not visible, and the uterus has a homogeneous echotexture with no uterine edema. Endometrial folds become edematous during estrus because of increased concentrations of circulating estrogen. The fluid-filled central portion of the fold is hypoechoic, whereas the hyperemic epithelial layer is hyperechoic. When the uterine horn is imaged as a cross-section, the appearance resembles a sliced orange or cartwheel (Figure 5.8-3). Occasionally free estrus fluid can be imaged.

It is possible to grade the degree of endometrial edema detected using a subjective scoring system (0-4) per the following:

Score	Appearance
0	No edema, with a typical homogeneous echotexture characteristic of diestrus
1	Smallest amount of readily detectable uterine edema
2	Moderate amount of edema throughout the whole uterus (see Figure 5.8-3)
3	Most obvious edema throughout the whole uterus, sometimes free fluid also noted (Figure 5.8-4)
4	Gross edema, rarely seen during the normal cycle.

Endometrial edema first becomes visible at the end of diestrus after luteal regression, becomes more prominent as estrus progresses, and generally decreases from 48 to 24 hours before ovulation. Edema may be detectable on the



**Figure 5.8-3** An ultrasound image (3- to 7-MHz transducer) of the uterine horn during estrus with a moderate amount of edema within the endometrium (score 2).



**Figure 5.8-4** An ultrasound image (5-MHz transducer, scale in cm) of the uterine body during estrus with a very obvious edema pattern and some free fluid (score 3).

day of ovulation, but this is always less than at some point earlier during estrus, and, in any case, edema never persists more than 36 hours after ovulation (unless it is pathologic).

The appearance of edema may precede the beginning of estrous behavior by 1, 2, or 3 days, although estrous behavior generally persists 1 day after edema disappears. In this author's experience edema is associated with basal (<1.0 ng/ml) progesterone values. It would therefore seem reasonable to attribute edema to increasing circulating estrogen concentrations. This means that detection of endometrial edema is a reliable indicator of estrus in the mare. This finding is particularly useful in mares not able to be teased with a stallion or which do not respond to teasing. However, it is known that nonhormonal influences, such as endometrial swabbing or breeding, can stimulate uterine edema. In addition, mares at the first

postpartum estrus (foal heat) have a more intense endometrial edema pattern, which may not decline as much as at subsequent estrus periods as ovulation approaches.

Mares that are susceptible to persistent postbreeding endometritis may ovulate with endometrial edema scores higher than normal. Susceptibility to postbreeding endometritis is known to involve fluid accumulation and possible lymphatic stasis; thus it is not surprising that edema scores are not as reliable in this category of mares. A small percentage of mares (5%) do not develop a detectable edema pattern during estrus.

In conclusion, the timing of ovulation in the mare is a key skill for the practitioner to acquire in working with mares. Detection of endometrial edema scores—along with accurate assessment of follicle size, shape, and texture—are the most helpful aids to determine the appropriate time to breed or inseminate the mare. Ideally these examinations should be performed on a regular basis.

### Supplemental Readings

- Chavatte P, Palmer E: Induction of ovulation in the mare. *Equine Vet Educ* 1998; 10:26-30.
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## CHAPTER 5.9

### Twins

GRANT S. FRAZER  
*Columbus, Ohio*

The diffuse microcotyledonary placentation of the mare makes it highly unlikely that a twin pregnancy will be carried to term. If the twin pregnancy is maintained until the latter part of gestation the placenta cannot meet the nutrient demands of the rapidly growing fetuses. Death of one or both fetuses is followed by abortion, with the characteristic avillous areas on the fetal membranes confirming the amount of placental disruption (Figure 5.9-1). Twin abortions in the last few months of gestation are likely to cause a dystocia. The live birth of twin foals is extremely uncommon, and many of these neonates do not survive. The mares are prone to fetal membrane retention and may be difficult to rebreed. Thus it is not surprising that the equine breeding industry has always tried to avoid twin pregnancies. This chapter will review the management options that are currently available.

#### MONITORING FOLLICULAR DEVELOPMENT AND OVULATION

A high incidence of twin ovulations occurs in some breeds, such as Thoroughbreds and warmbloods, and mares that tend to double ovulate can be expected to do this repeatedly. Thus a mare with a tendency to double-ovulate should have this information noted prominently on her breeding record. Most twin pregnancies arise from such double ovulations. Owners need to appreciate that these double ovulations are generally asynchronous and may be

separated by a couple of days. If a fertile stallion was used to breed the mare on the first ovulation, it is possible that viable sperm will still be present in the reproductive tract when the second oocyte arrives. This possibility must be remembered when scanning mares for pregnancy at 14 to 16 days. At that time, it is good practice to scan the ovaries for evidence of luteal tissue from a second ovulation.

In the past, one strategy that was employed when a veterinarian palpated two large (>30 mm) follicles was to wait to breed until the next cycle. This approach wasted valuable days in the breeding season, and many of these mares would repeat the same follicular process during the next cycle. An alternate approach was to hope that the second follicle would continue to develop for 10 to 12 hours after the first detected ovulation. Because the ovulated oocyte is unlikely to be viable at this time, a delayed breeding could be performed in anticipation of the second ovulation. Today the preferred strategy is to breed all eligible mares—irrespective of the number of preovulatory follicles. The widespread adoption of early ultrasonographic pregnancy examinations has permitted the focus to be placed on embryonic vesicle reduction once the presence of a twin pregnancy has been confirmed.

#### MANUAL REDUCTION

The increasing size of the embryonic vesicle, coupled with the increasing tone of the early pregnant uterus, tends to

postpartum estrus (foal heat) have a more intense endometrial edema pattern, which may not decline as much as at subsequent estrus periods as ovulation approaches.

Mares that are susceptible to persistent postbreeding endometritis may ovulate with endometrial edema scores higher than normal. Susceptibility to postbreeding endometritis is known to involve fluid accumulation and possible lymphatic stasis; thus it is not surprising that edema scores are not as reliable in this category of mares. A small percentage of mares (5%) do not develop a detectable edema pattern during estrus.

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The diffuse microcotyledonary placentation of the mare makes it highly unlikely that a twin pregnancy will be carried to term. If the twin pregnancy is maintained until the latter part of gestation the placenta cannot meet the nutrient demands of the rapidly growing fetuses. Death of one or both fetuses is followed by abortion, with the characteristic avillous areas on the fetal membranes confirming the amount of placental disruption (Figure 5.9-1). Twin abortions in the last few months of gestation are likely to cause a dystocia. The live birth of twin foals is extremely uncommon, and many of these neonates do not survive. The mares are prone to fetal membrane retention and may be difficult to rebreed. Thus it is not surprising that the equine breeding industry has always tried to avoid twin pregnancies. This chapter will review the management options that are currently available.

#### MONITORING FOLLICULAR DEVELOPMENT AND OVULATION

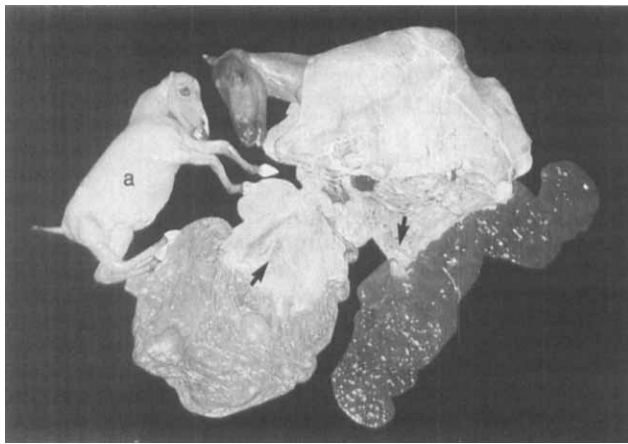
A high incidence of twin ovulations occurs in some breeds, such as Thoroughbreds and warmbloods, and mares that tend to double ovulate can be expected to do this repeatedly. Thus a mare with a tendency to double-ovulate should have this information noted prominently on her breeding record. Most twin pregnancies arise from such double ovulations. Owners need to appreciate that these double ovulations are generally asynchronous and may be

separated by a couple of days. If a fertile stallion was used to breed the mare on the first ovulation, it is possible that viable sperm will still be present in the reproductive tract when the second oocyte arrives. This possibility must be remembered when scanning mares for pregnancy at 14 to 16 days. At that time, it is good practice to scan the ovaries for evidence of luteal tissue from a second ovulation.

In the past, one strategy that was employed when a veterinarian palpated two large (>30 mm) follicles was to wait to breed until the next cycle. This approach wasted valuable days in the breeding season, and many of these mares would repeat the same follicular process during the next cycle. An alternate approach was to hope that the second follicle would continue to develop for 10 to 12 hours after the first detected ovulation. Because the ovulated oocyte is unlikely to be viable at this time, a delayed breeding could be performed in anticipation of the second ovulation. Today the preferred strategy is to breed all eligible mares—irrespective of the number of preovulatory follicles. The widespread adoption of early ultrasonographic pregnancy examinations has permitted the focus to be placed on embryonic vesicle reduction once the presence of a twin pregnancy has been confirmed.

#### MANUAL REDUCTION

The increasing size of the embryonic vesicle, coupled with the increasing tone of the early pregnant uterus, tends to



**Figure 5.9-1** These twin fetuses were aborted after one died and became partially mummified (*a*). The mare dripped mammary secretions for several days before aborting. Note the alvilous areas (*arrows*) on both chorioallantoic membranes.

fix the conceptus at the base of one uterine horn by day 16. It is essential that the ultrasound scan of the uterus be thorough, with a complete examination of the length of both horns plus the uterine body as far back as the cervix. This is especially important before day 16 because the vesicle moves freely within the lumen of both horns and the uterine body. The advantage of these early scans is that if twin vesicles are detected it will be easier to manually separate them before day 16. Successful elimination of one vesicle is more likely at that time because the uterine walls are thin, and minimal pressure is required to crush a vesicle. A definite “pop” can be felt when the vesicle ruptures, but success should always be confirmed by ultrasound.

The downside to this approach is that an early embryonic vesicle can easily be confused with an endometrial cyst. The embryo itself does not become readily identifiable until the fourth week of pregnancy. Thus it is good practice to note the size and location of any cysts at the time the mare is being examined for breeding. However, it is not an uncommon occurrence that the veterinarian doing the early (14-16 days) pregnancy scan will be examining the mare for the first time. If no record of cyst size and location exists, it is virtually impossible to differentiate twin vesicles from a singleton and a cyst with a single examination. This is especially true because asynchronous ovulations are likely to result in considerable size discrepancy between the two vesicles. Under these circumstances it may be best to measure each suspect vesicle and note its location. A second scan in 1 to 2 days should note a size increase in any normally growing vesicle (~4 mm/day). Only then can a confident decision be made about attempting to “pinch” one of the growing vesicles. Unfortunately this delay may make separation of unilaterally fixed vesicles more difficult because of their ongoing growth and the increased uterine tone.

Manual reduction of bilaterally fixed vesicles requires less manipulation than with unilateral twins. It is a relatively easy procedure, and success rates exceeding 90% are not uncommon if the vesicle is crushed before day 16. If the vesicles are unilaterally fixed, the clinician should attempt to move the more proximal vesicle away towards the

tip of the uterine horn. At this location the manual reduction procedure is less likely to disrupt the remaining vesicle. The vesicle can be crushed by pinching it between the thumb and fingers. Alternately, the vesicle is squeezed against the mare’s pelvis until it ruptures. If the twins can be separated before crushing, the success rate may be similar to that for reduction of bilateral twins. If the unilateral twins cannot be separated or are greater than 20 days’ gestation, the success rate is lower. The extra pressure used to eliminate a twin vesicle after fixation is the reason many clinicians will accompany reduction with antiinflammatory medications and progestin therapy. The likelihood of success improves with experience, and some clinicians develop a reputation for being especially adept at the procedure. Obviously the nature of the mare is an important factor, and those that strain excessively can make the procedure extremely difficult. If the unilateral vesicles are not detected until after day 20, manipulations can easily result in the disruption of both vesicles. The best option in these cases may be to wait and see whether natural reduction occurs.

## NATURAL REDUCTION

Almost three quarters (70%) of twin embryonic vesicles become fixed unilaterally; only 30% of twin vesicles become fixed bilaterally. The advantage of this probability is that natural reduction to a single pregnancy is far more likely with unilaterally fixed vesicles. Over 80% of unilaterally fixed twins are likely to naturally reduce to a singleton, with over half of these occurring between days 16 and 20. On the other hand, the majority of bilaterally fixed vesicles will continue to develop. Late in the season these odds play an important part in any informed discussion about management options. Early in the season most veterinarians will opt to attempt reduction, knowing that if both vesicles are lost that it will still be possible to rebreed the mare. Close to the end of the season an unsuccessful attempt at reduction may preclude the mare from being rebred. If natural reduction does not occur by day 30, the advent of transvaginal reduction has opened a window for later attempts at reduction. If this fails, owners may opt to put the mare under lights and breed her early next season rather than be locked into a pattern of late foals.

## PREGNANCY TERMINATION WITH PROSTAGLANDIN

If natural reduction does not occur, terminating the pregnancy with a prostaglandin injection is always possible. This will cause lysis of the corpora lutea that resulted from the double ovulation, and the precipitous decline in progesterone will bring the mare back into estrus. However, this treatment must be given before day 35. Once the endometrial cups form it may take repeated injections to terminate the pregnancy, and the mare is unlikely to return to estrus until the cups are sloughed. The endometrial cups originate from specialized fetal trophoblast cells. They secrete equine chorionic gonadotropin (eCG), a hormone that causes the development of accessory corpora lutea and thus augments the progesterone level in support of the early pregnancy.

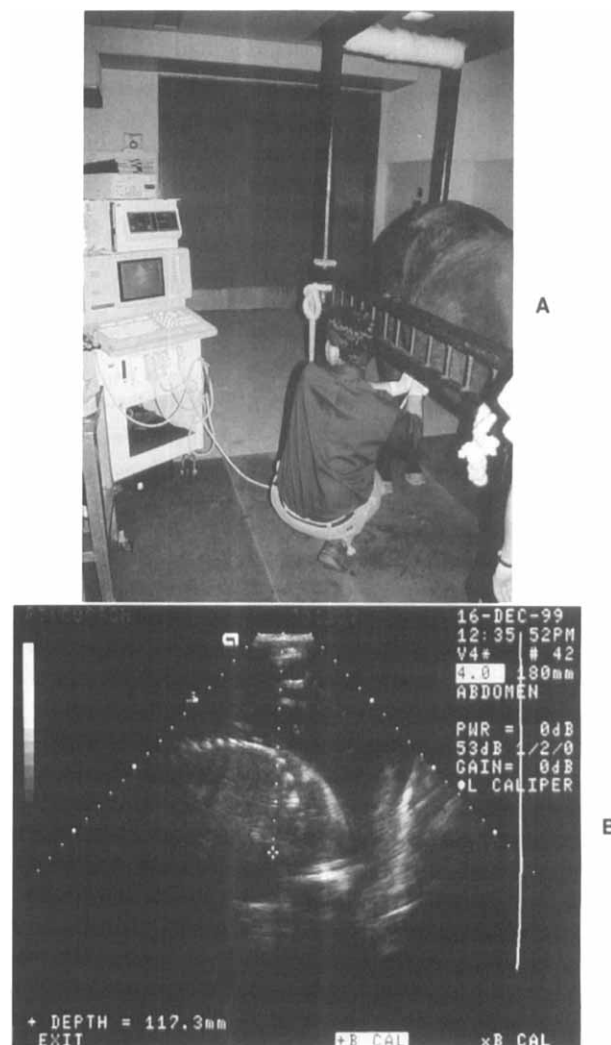
## TRANSVAGINAL ULTRASOUND-GUIDED ALLANTOCENTESIS

Although the advent of transrectal ultrasonography has dramatically improved the ability of veterinarians to make an early diagnosis of twin pregnancies, diagnostic errors still occur. This could be due to an early pregnancy diagnosis when the second vesicle was too small to detect, incomplete examination of the entire uterus, poor image quality, or an inability of the clinician to differentiate two embryonic vesicles that are closely apposed to each other. If natural reduction does not occur or the diagnosis of twins is not confirmed until after 30 days, transvaginal aspiration of one vesicle is an option. The results are best if the procedure is performed before day 35. Although spontaneous reduction of twin pregnancies can occur even after day 40, the probability is low. Natural twin reduction is more likely to occur if an obvious size discrepancy is present between the two vesicles at this time.

If a transvaginal reduction is to be attempted, the mare should be treated with flunixin meglumine. Many clinicians will also administer oral altrenogest. Because sedation causes significant uterine relaxation, most clinicians use a lidocaine enema to reduce straining. The transvaginal aspiration technique employs a 5.0- or 7.5-MHz endovaginal curvilinear transducer. The transducer and casing should be cold-disinfected or sterilized before use. The assembled unit is then placed in a sterile transducer cover that has been filled with sterile lubricating gel. The transducer is advanced aseptically until it is seated lateral to the cervix. The clinician then grasps the pregnancy per rectum and advances a sterile 60-cm, 18-gauge spinal needle with an echogenic tip along the needle guide in the transducer casing. A dotted line on the ultrasound screen can be used to select a path for the needle entry into the embryonic vesicle. A sharp jab of the needle penetrates the vaginal wall, peritoneal lining, uterus, and ultimately the allantoic or yolk sac. A 60-ml syringe is attached to the needle, and the embryonic fluid aspirated. Aspiration should be stopped when danger of damaging the adjacent vesicle of unilateral twins arises. If a bilateral twin is being eliminated, the needle can be moved within the vesicle until all detectable fluid has been aspirated. The success rate is better for bilateral twin reductions. Death of the remaining twin is most likely to occur within 2 weeks of the procedure. Although reports are scarce, preliminary data suggest that experienced operators may achieve a live singleton birth in about one third of cases.

## TRANSABDOMINAL ULTRASOUND-GUIDED FETAL CARDIAC PUNCTURE

In advanced twin pregnancies, attempting reduction by a transabdominal approach is possible. Fetal intracardiac injection of potassium chloride is effective but requires accurate placement of the KCl into the fetal heart. Best results are obtained when the pregnancy is between 115 and 130 days. At this stage experienced operators can achieve a 50% success rate. Procaine penicillin G can cause fetal death when injected into either the fetal thorax or abdomen, but the effect is not instantaneous. The advantage of the latter treatment is that it does not require precise placement of the injection into the fetal heart. Mares



**Figure 5.9-2** **A**, A 3.0-MHz transducer can be used to image the 90- to 130-day fetus in the caudal abdomen, just cranial to the udder. **B**, Some clinicians prefer a free-hand injection technique, whereas others use a transducer fitted with a biopsy guide. Note the characteristic image of the fetal thorax. The dotted line indicates the path along which the aspiration needle travels as it advances into the fetal heart.

should be started on oral altrenogest, systemic antibiotics, and flunixin meglumine on the day of the procedure. The antibiotic coverage and antiinflammatory medication should be continued for 3 days.

A 3.0-MHz transducer can be used to image the 90- to 130-day fetus in the caudal abdomen, just cranial to the udder (Figure 5.9-2). Once the mare has been sedated, the uterus will relax, and the location of the fetuses will shift cranially. A sedative/analgesic combination that works well for this procedure is acepromazine (10 mg), xylazine (100 mg), and butorphanol (10 mg). The smallest and/or most easily accessible fetus is selected for reduction. The ventral abdomen should be surgically prepared, and local anesthetic infiltrated at the puncture site. Some clinicians are adept at a "free-hand" injection technique, whereby the fetus is injected by merely observing the ultrasound image. Others prefer to use an ultrasound transducer that is fitted with a biopsy guide. An 18-gauge, 6- to 8-inch



spinal needle with stylet can be used for most fetal injections. The distance from the skin surface to the fetus determines the length of the needle that is required. Specialized needles with echogenic tips are available to provide better visualization via ultrasound. Once the location of the selected twin's thorax is confirmed, the needle is introduced through the prepared skin, abdominal wall, and uterus. If procaine penicillin G is to be injected, the needle may puncture either the fetal thorax or abdomen. Up to 20 ml is typically injected into the fetus. Fetal death should be confirmed the following day.

Although the benefits of supplemental progestin therapy are debatable, many clinicians suggest that the mare be medicated for at least 2 weeks if the initial twin reduction has been successful. It is essential that fetal viability be checked regularly because supplemental progestin therapy may prevent elimination of the dead fetuses if both die. Most abortions will occur within 1 to 2 months after the reduction procedure. Survival of the remaining twin seems to depend somewhat on the amount of endometrial surface that was its domain before the reduction. If the operator is experienced in the technique, between

30% and 60% of cases can be expected to deliver a singleton foal, although the ultimate size and viability may be suboptimal. The eliminated twin in these cases can be seen as a mummified remnant contained within an invaginated pouch that protrudes into the allantoic space of the viable foal's fetal membranes.

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## CHAPTER 5.10

# Foal Heat-Breeding

WALTER W. ZENT  
*Lexington, Kentucky*

Commercial horse breeding farms operate under the same economic rules as other forms of intensive livestock production. Use of stallions must be efficient, and mares must produce the greatest number of foals possible. This requires intensive management. The primary reason for foal heat-breeding is to increase the efficiency of the production unit.

The performance of a herd of mares should be measured not only by the final conception rate but also by how efficiently that pregnancy rate was achieved. This can be measured by the number of breedings per conception and by noting when in the breeding season each mare becomes pregnant. A set of criteria can be established such that the performance of individual mares and the herd can be measured against the ideal. The criteria can be flexible and should be tailored to meet the economic objectives of the operation. For example, the time at which the farm would like the earliest foal to be born is determined by the management practices of that farm and by the requirements of a particular breed registry. Once these criteria are established, a management goal can be set. In central Kentucky the main commercial business is the production and sale of Thoroughbred yearlings. Thus a workable criterion is that no mare is bred before the fif-

teenth of February. Optimal fertility dictates that no mare is bred before the tenth day after foaling. That means that all maiden, barren, and January foaling mares should be bred as close to the fifteenth of February as possible. All other foaling mares are bred on or soon after the tenth day from foaling. Of course, this schedule is not always possible, nor in many instances is it advisable. However, if management strives to meet these goals, the net result will be that the farm can push foaling dates to the front of the season. This shift will result in increased production from the mare herd. It can be readily seen that foal heat-breeding plays an important part in such a strategy because it keeps the interval between foaling dates to a minimum.

### SELECTION OF MARES

The success of breeding mares soon after foaling depends on several factors. The most important of these is correct selection of the mares to be bred. If the mare fails to become pregnant, resorbs, or aborts the fetus, nothing has been gained by the foal heat-breeding. Actually, the ultimate date of conception may be significantly delayed. If the breeding is successful, the mare will produce an earlier foal next year, thus moving her forward in the breed-



spinal needle with stylet can be used for most fetal injections. The distance from the skin surface to the fetus determines the length of the needle that is required. Specialized needles with echogenic tips are available to provide better visualization via ultrasound. Once the location of the selected twin's thorax is confirmed, the needle is introduced through the prepared skin, abdominal wall, and uterus. If procaine penicillin G is to be injected, the needle may puncture either the fetal thorax or abdomen. Up to 20 ml is typically injected into the fetus. Fetal death should be confirmed the following day.

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ing season. If this approach is to be efficient, mares must be selected carefully and should meet specific criteria to become eligible for breeding on their foal heat.

If a mare is to be bred on the foal heat, she must have foaled during a time of year when breeding is appropriate. Obviously a mare that foals in January would not be eligible to be bred because she might foal before the end of the same year. Young mares are generally better candidates than old mares because they usually recover sooner from foaling. Each mare's previous gestational lengths should be considered because mares will usually follow the same pattern each year. For example, if a mare foals at ten and a half months in a given year, it is often a repeated pattern. Thus farm managers must be careful not to breed such mares too early. Mares that foal earlier in the breeding season are often better candidates to be bred on the foal heat than those mares that foal late in the season. Late-foaling mares are usually problem breeders and are often less fertile than mares that foal earlier in the season.

Mares that are candidates for foal heat-breeding include those that have not had a difficult delivery, retained fetal membranes, metritis, or other complications associated with foaling. All mares should be examined soon after foaling. A decision can then be made as to whether a mare is in suitable condition to be bred. The ability of mares to recover from foaling can be quite variable. Some mares that do not appear to be ready to breed may actually recover very well. It is best to specify a certain postpartum period during which all foaling mares will be examined. If a management routine is established, mares are less likely to be overlooked. It is important to examine all mares around the time of foal heat, even if they are not going to be bred at the time. Problems associated with foaling are often found during these exams. Prompt therapy can ensure that the mare will be ready to be bred during the next heat period. Either day 7 or day 8 after foaling is typically chosen for this evaluation. The mares are usually in estrus at this time and have had time to substantially recover from foaling. If the mare is to be bred, the seventh or eighth day after foaling will usually ensure that the management has time to arrange a mating.

### Clinical Examination

The examination of the mare after foaling should proceed in an orderly fashion so that nothing is omitted. After an external inspection of the vulva, the vagina and cervix are examined through a speculum. After palpation per rectum, the uterus and ovaries should be examined by ultrasound. The vulva and vestibule are examined visually for the presence of lacerations, hematomas, and abscesses. The vagina should be examined carefully for the presence of rectovaginal fistulas, lacerations, and evidence of urine pooling. The cervix must be inspected closely for lacerations, and any question about its integrity merits a digital examination to make sure that the cervix is competent. In some mares the cervix may be pulled down and forward. This finding is usually a sign that the uterus is still large. The color of the vaginal and cervical mucous membranes should be noted, as should the nature of the cervical mucus. If the mucosa is inflamed or if the cervical mucus is cloudy, the mare may have endometritis. Culture and cy-

tologic evaluation of the uterus should be performed (see Chapter 5.2: "Endometrial Culture").

Palpation per rectum can determine the size of the uterus and ovaries. The presence of masses or other abnormalities in the pelvis and broad ligament should be noted. An ultrasound examination allows the clinician to visualize the ovaries and uterus. The ovaries are examined for the presence of follicles, hematomas, and tumors. Granulosa cell tumors commonly develop during pregnancy and can be detected at the postpartum examination. The ultrasound examination permits visualization of hematomas in the broad ligament or in the uterine wall, and the presence of fluid in the uterine lumen can be determined. If the uterus has a discernable amount of fluid, a uterine culture should be performed. Once the examination is completed a decision can be made as to whether the mare should be bred on her foal heat. Results from the culture will aid in developing a therapeutic plan.

### DETERMINING AN APPROPRIATE TIME TO BREED THE MARE

Mares that are normal and eligible to be bred on the foal heat can then be monitored for follicular development and bred at the optimal time. Several studies have shown that time of ovulation is critical to the success of foal heat-breeding. Mares that ovulate before ten days after foaling have a much lower pregnancy rate than do mares that ovulate at 10 days or later. Therefore if ovulation occurs too early, it is better not to breed the mare even if she is deemed suitable for mating. The performance of the herd will be better if these mares are not bred at the foal heat and then are managed so that they can be bred at the earliest time possible after this first ovulation.

If a decision has been made to skip the foal heat, these mares may be bred earlier by using prostaglandin to cause regression of the corpus luteum. The prostaglandin can be given at day six or seven postovulation, and the mare will often be ready to breed six or seven days later. This will shorten the time from foaling to breeding by about a week compared to allowing the mare to return to heat naturally. Mares that have a uterine infection, have fluid in their uteri, or have poor uterine involution after foaling often will also benefit from prostaglandin therapy. The early return to estrus appears to have a cleansing effect on the reproductive tract of these mares. It also gives the veterinarian a chance to continue therapy if necessary.

Some managers use hormonal therapy to delay the onset of the first estrus and thus ensure that the ovulation will occur ten days or more after foaling. Two methods are used to achieve this delay. One is with the use of oral altrenogest, and the other with the use of injectable progesterone and estradiol. Although the altrenogest (0.044 mg/kg) is the simplest and most readily available product, it is also the least precise. The progesterone (150 mg) estradiol-17 $\beta$  (10 mg) in oil combination provides more precise control of follicular development but must be given by daily injections and thus can cause some muscle soreness. Irrespective of the method chosen, beginning treatment on the first day postfoaling is important. If treatment is begun later—after follicular development has commenced—it may be difficult to suppress this growth,

and some mares will continue through the therapy and ovulate. Mares that are successfully managed in this manner can be made to ovulate at day ten, twelve, or even later from foaling. Some investigators believe that this can be helpful. However, a controlled study in which this author participated showed very little benefit over the intensive management of foal heat alone.

### CARE OF THE MARE AFTER BREEDING

Mares bred on foal heat should be examined the day after breeding—not only to confirm ovulation but also to ensure that the uterus has not retained a significant amount of fluid. If an ultrasound examination reveals an echogenic fluid accumulation, the mare should be treated with oxytocin to help promote elimination of this fluid. If a large volume of fluid is present, it may be advisable to lavage the uterus. Postbreeding antibiotic infusion may also be indicated in foal heat mares—more so than at other times. If

the mare requires a Caslick operation, it should be performed at this time. The mare is less forgiving at the foal heat than during later estrous periods. Thus attention to detail is especially important.

Foal heat-breeding is a useful management tool, but it must be done carefully and with thought. Indiscriminate foal heat-breeding can often be detrimental to the mare and thus make the overall management program less efficient.

### Supplemental Readings

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## CHAPTER 5.11

# Thyroid Function and Fertility

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CYNTHIA V. GUTIERREZ

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The relationship between thyroid dysfunction and fertility in the mare has not been clearly defined. Many questions remain unanswered, particularly concerning the role that hypothyroidism plays in infertility. Most of these uncertainties stem directly from the inability to accurately diagnose thyroid diseases. Currently, routine diagnostic tests are either not available or fraught with inadequacies. Historically, practitioners have relied principally on serum T4 (thyroxine) and T3 (triiodothyronine) concentrations and clinical signs, if present, to arrive at a presumptive diagnosis of hypothyroidism. The possible effects of hypothyroidism on fertility in horses have been extrapolated from human research. Hypothyroidism has been shown to cause infertility in women and laboratory animals. However, in both cases the incidence of true thyroid dysfunction appears to be low. The incidence of hypothyroidism in adult horses is estimated to be extremely low. Therefore the probability that a mare is infertile as a result of thyroid dysfunction should be viewed as being remote. Hyperthyroidism has not been reported or studied in horses, but it is thought to be rare.

### DIAGNOSTIC TESTS

The diagnostic tests available for evaluating thyroid function are limited. The test most commonly used in private practice is the serum T4 and T3 test. Numerous studies

have shown these tests to be inaccurate and poor indicators of thyroid function. They also are influenced readily by many nonthyroidal factors. Thus the results of the T4 and T3 tests should be interpreted cautiously and never used as the sole criteria for making a diagnosis.

In human medicine, measurement of both T4 concentration and thyroid-stimulating hormone (TSH) provides almost 100% accuracy in achieving a diagnosis of thyroid disease. Currently, no commercially available assays to measure equine TSH can be found. A few laboratory companies offer TSH assays, but none of these laboratories have validated the equine assay. Equine TSH has been available to selective research projects. These projects have shown that the measurement of TSH in conjunction with thyroid hormones is useful in the diagnosis of equine hypothyroidism. Performance of both tests enables an accurate diagnosis (see Chapter 15.1: "Thyroid Dysfunction"). This would enable practitioners to identify those horses with a true deficiency and thus in need of exogenous thyroid supplementation. Likewise, accurate diagnostic tests would minimize oversupplementation of horses that have normal thyroid function.

Another test advocated for the diagnosis of hypothyroidism is the measurement of free thyroid hormones (fT4, fT3). Laboratories promote these assays because they should account for many of the nonthyroidal factors that plague the serum T4 and T3 tests. Equilibrium dialysis and

and some mares will continue through the therapy and ovulate. Mares that are successfully managed in this manner can be made to ovulate at day ten, twelve, or even later from foaling. Some investigators believe that this can be helpful. However, a controlled study in which this author participated showed very little benefit over the intensive management of foal heat alone.

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The relationship between thyroid dysfunction and fertility in the mare has not been clearly defined. Many questions remain unanswered, particularly concerning the role that hypothyroidism plays in infertility. Most of these uncertainties stem directly from the inability to accurately diagnose thyroid diseases. Currently, routine diagnostic tests are either not available or fraught with inadequacies. Historically, practitioners have relied principally on serum T4 (thyroxine) and T3 (triiodothyronine) concentrations and clinical signs, if present, to arrive at a presumptive diagnosis of hypothyroidism. The possible effects of hypothyroidism on fertility in horses have been extrapolated from human research. Hypothyroidism has been shown to cause infertility in women and laboratory animals. However, in both cases the incidence of true thyroid dysfunction appears to be low. The incidence of hypothyroidism in adult horses is estimated to be extremely low. Therefore the probability that a mare is infertile as a result of thyroid dysfunction should be viewed as being remote. Hyperthyroidism has not been reported or studied in horses, but it is thought to be rare.

### DIAGNOSTIC TESTS

The diagnostic tests available for evaluating thyroid function are limited. The test most commonly used in private practice is the serum T4 and T3 test. Numerous studies

have shown these tests to be inaccurate and poor indicators of thyroid function. They also are influenced readily by many nonthyroidal factors. Thus the results of the T4 and T3 tests should be interpreted cautiously and never used as the sole criteria for making a diagnosis.

In human medicine, measurement of both T4 concentration and thyroid-stimulating hormone (TSH) provides almost 100% accuracy in achieving a diagnosis of thyroid disease. Currently, no commercially available assays to measure equine TSH can be found. A few laboratory companies offer TSH assays, but none of these laboratories have validated the equine assay. Equine TSH has been available to selective research projects. These projects have shown that the measurement of TSH in conjunction with thyroid hormones is useful in the diagnosis of equine hypothyroidism. Performance of both tests enables an accurate diagnosis (see Chapter 15.1: "Thyroid Dysfunction"). This would enable practitioners to identify those horses with a true deficiency and thus in need of exogenous thyroid supplementation. Likewise, accurate diagnostic tests would minimize oversupplementation of horses that have normal thyroid function.

Another test advocated for the diagnosis of hypothyroidism is the measurement of free thyroid hormones (fT4, fT3). Laboratories promote these assays because they should account for many of the nonthyroidal factors that plague the serum T4 and T3 tests. Equilibrium dialysis and

ultrafiltration are considered accurate techniques for measuring free thyroid hormones. Unfortunately most commercial laboratories do not offer these techniques and rely instead on analogue methods. Studies have shown that these analogue methods provide no more useful information than the standard serum T4 test.

Many studies have been done on adult horses to investigate the causes of hypothyroidism and to document normal thyroid hormone concentrations in open mares, pregnant mares, and the levels before parturition. The relationship between T4 concentration and fertility in mares also has been studied. One study demonstrated that thyroidectomized mares ( $n = 2$ ) were still able to conceive and carry normal foals to term. Studies concerning hypothyroidism in stallions are not readily found. In humans, hypothyroid men are often impotent or have decreased fertility. The extent to which hypothyroidism contributes to infertility continues to be unknown until validated tests are developed for measuring both thyroid hormones and equine TSH. Once these tests are available, further studies will be required to investigate any hypothyroidism related fertility issues in mares and stallions. Results of such studies may help establish an accurate relationship between hypothyroidism and infertility and would more accurately indicate the need for supplementation.

## INDICATIONS FOR TESTING

Currently thyroxine (T4) concentrations are determined routinely in broodmares, and many with a low T4 value are put on exogenous thyroxine supplementation. Such therapy is due to a perception that the test confirms the presence of a thyroid hormone deficiency. Some broodmare farms have even incorporated the T4 test as a routine part of their breeding program. Concern about the scientific validity of this practice persists, and the cost-to-benefit ratio remains in question. In years past, the annual cost of exogenous thyroid hormone supplementation was estimated at \$750,000 per year. Today, that estimate would far exceed \$1 million per year. The laboratory expenses incurred by thyroid hormone assays, and the expense of hormone supplementation, increase the cost and complexity of foal production—with questionable benefit. In fact, a recent study has shown that performance of T4 tests as a routine part of a breeding program in an attempt to increase pregnancy rates is not justified. Therefore T4 testing should be used only for specific cases in which it is clinically indicated.

Mares that are infertile but are not exhibiting any clinical signs associated with hypothyroidism should be first examined for other potential causes of infertility before testing. The typical clinical signs associated with hypothyroidism include a thick "cresty" neck, obesity, dull haircoat, and/or laminitis. Mares that are infertile and exhibit these signs can be considered possible hypothyroid candidates. These mares also should have been carefully examined previously for other causes of infertility.

Other endocrine disorders should be considered and ruled out before resorting to T4 testing. Many factors are involved in the process of conception, and thus infertility can be difficult to assess based on only one parameter. Routine T4 testing of healthy broodmares before the

breeding season is not helpful in predicting which mares could potentially be problem breeders later in the season.

## TREATMENT

The occasional mare that does fit the above criteria should be tested. If T4 concentrations in these mares are low then a presumptive diagnosis of hypothyroidism can be made. These mares may be placed on thyroxine supplementation and monitored for signs of clinical improvement. The recommended dosage for oral thyroxine supplementation (l-thyroxine) is 0.5 to 3 mg/45 kg once daily. This supplement comes in a powder form and is administered by teaspoons. One level teaspoon is equal to 12 mg of supplement. A 500-kg (1100-lb) mare would receive approximately two teaspoons of supplement. A mare should respond to supplementation in approximately 6 weeks. The response to treatment can be monitored clinically or by measuring serum T4 levels. The diagnosis of hypothyroidism should be reconsidered if a mare does not respond in that time.

Veterinarians should understand that recent studies have concluded that exogenous thyroxine supplementation of mares, based solely on a low serum T4 value, is not indicated. Such supplementation is unlikely to be beneficial. Anecdotal reports exist of exogenous thyroxine supplementation possibly enhancing fertility in mares that tested low but were not necessarily considered to be hypothyroid. Once again, studies have shown that this is not true. Supplementation of mares based principally on a low serum T4 value apparently does not enhance fertility. Furthermore, suppression of normal thyroid hormone production is theoretically possible in mares that have a normal pituitary-thyroid axis. Supplementation of a normal horse could result in iatrogenic hypothyroidism resulting from negative feedback on a healthy pituitary gland. Thus exogenous thyroxine supplementation should be instituted only in those mares that are demonstrating clinical signs, have a low serum T4 levels, and have been examined carefully to rule out other potential causes of infertility.

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## CHAPTER 5.12

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# Management of Stallions for Artificial Breeding

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The management of stallions used in an artificial insemination program must be tailored to the individual stallion and to the facilities and personnel at the breeding farm. The stallion owner, farm manager, and veterinarian should develop a coordinated plan to optimize the stallion's health for his athletic and breeding careers, to coordinate the housing and movement of all horses on the farm, to utilize farm personnel efficiently, to achieve a high level of fertility in an efficient manner, and to minimize risks to the stallion, personnel, and individual mares. A unique plan must be developed for a stallion being used in a breeding program but which is still actively competing in his athletic discipline. The health and breeding program must address the needs of the stallion based on his age, existing disease conditions such as orthopedic problems, location and number of mares to be bred, semen quality, and the innate fertility of the stallion.

### GENERAL HEALTH CONSIDERATIONS

The nutritional needs of the stallion used in an artificial insemination (AI) program are not unique. The goal of the feeding program should be to maintain the stallion at an ideal weight and fitness. Pasture, good quality grass or grass-alfalfa mixed hay, and water should be available at all times. Grain supplementation may be necessary to provide adequate vitamin and mineral consumption not supplied by hay. If the stallion is fed a balanced ration, it is unlikely that additional supplementation of the ration will increase fertility or daily sperm production. The stallion's feeding program should be associated with an exercise program to keep the horse alert, athletic, and content.

A stallion needs daily exercise in a paddock or small pasture. If the stallion does not exercise freely during turnout time, it may be necessary to ride, drive, hand walk, or lunge the horse daily to maintain the stallion's athleticism and body condition. A stallion needs exercise even during inclement weather. Many objectionable stallion behaviors are associated with a poorly implemented nutrition and exercise program.

Breeding stallions should be dewormed at regular intervals along with all the other horses on a farm. Fecal exams can be performed periodically to ensure the effectiveness of the parasite control program. To this author's knowledge, reproductive performance of stallions has not been altered by regular use of commonly available deworming compounds.

Yearly dental examinations should be performed to maintain normal mastication. Dental procedures should be carried out as needed. However, if tranquilization is required, promazine tranquilizers should not be used because of the risk of penile paralysis.

The farrier should evaluate the stallion's feet at regular intervals of 6 to 8 weeks. Stallions receiving adequate turnout, frequently require minimal hoof trimming. Problems such as prior athletic injury, laminitis, hoof-wall cracks, flat soles, and underrun heels may require evaluation and treatment by the farrier and veterinarian to maintain hoof health and stallion longevity.

In general, stallions should be vaccinated against tetanus, eastern and western encephalomyelitis, and rabies. Many other vaccines are available and may be appropriate for use in individual stallions, based on age, horse farm population density, current farm disease status, and other factors. The vaccination program should be designed for the individual farm and stallion. Vaccinations against upper respiratory tract infections also should be considered for most active, breeding stallions. Maintaining immunity against influenza, rhinopneumonitis, and strangles may prevent infections with these viruses and bacteria and minimize the adverse effect of elevated body temperature on spermatogenesis and semen quality. Special effort should be made to use vaccines containing the most current serovars of influenza and rhinopneumonitis viruses. Other vaccines that should be considered based on disease prevalence at the farm include botulism and Potomac horse fever (*Neorickettsia risticii*).

Currently, a provisional license has been granted for the production of a vaccine against equine protozoal myeloencephalitis (*Sarcocystis neurona*) and West Nile virus encephalitis. Data are not available, at this time, to fully support the efficacy of these vaccines and potential adverse effects on breeding stallions. Consideration of the use of these vaccines in endemic regions of the country may be necessary.

Equine arteritis virus (EAV) can be spread from stallions to mares via respiratory tract secretions but, more commonly, through semen. Approximately 30% of stallions seropositive for EAV shed virus in their semen. Virus may be shed in the semen of an infected stallion for a short period of time or a lifetime. This virus can cause upper respiratory infections and abortion. All stallions used in an AI program should be tested serologically for EAV antibodies. A serologically negative stallion can be used to

breed seropositive or seronegative mares without risk. If the stallion is seropositive for EAV antibodies, an aliquot of semen from one or more ejaculates should be submitted to the diagnostic laboratory for virus isolation. If the stallion is actively shedding virus in his semen, he should be used to inseminate only naturally exposed or vaccinated seropositive mares. Equine arteritis virus can infect mares inseminated with fresh, cooled, or frozen semen.

The use of the polymerase chain reaction (PCR) testing of semen for EAV is not accurate in determining the presence of virus in semen. If a stallion is determined to be serologically negative for EAV antibodies, vaccination against EAV should be strongly considered. Vaccination of the seronegative stallion prevents development of the carrier state if the stallion is exposed to field strain virus. However, vaccination apparently does not alter the carrier state once infection has been established. Vaccination of stallions against EAV should occur at least 30 days before the onset of the breeding season. The seropositive stallion that does not shed virus in his semen can be used safely in an AI program using fresh, cooled, or frozen semen. All stallions used for breeding should be tested annually for equine infectious anemia.

The economic value and importance of the stallion to a breeding program may be substantial. Many stallion owners elect to insure the stallion with mortality and/or fertility policies. These policies are not necessarily standardized but may include physical examination of the stallion and historical fertility data. A breeding soundness evaluation usually is not required.

## BREEDING SOUNDNESS EVALUATION

A thorough breeding soundness evaluation should be performed on stallions entering an AI program. This evaluation should be done before purchase and before the onset of each breeding season. The purpose of the evaluation is to assess any physical limitations to breeding. The stallion's willingness and manner of mounting an estrous mare or phantom should be assessed. Seminal quality should be determined. Specifically, the number of sperm ejaculated, percentage and type of sperm motility, morphologic analysis of sperm, bacteriologic and, possibly, viral status of the semen are determined. The longevity and type of sperm motility in semen extenders also should be determined. Any evidence of physical abnormalities or lesions of the external and internal genitalia should be noted.

The evaluation of semen quality may require the collection of numerous ejaculates of semen. The seminal quality of initial ejaculates from sexually rested stallions may not be representative of the stallion's seminal quality while in routine use. The semen from sexually rested stallions frequently has markedly elevated sperm numbers, reduced sperm motility, poor longevity of sperm motility under shipped, cooled semen conditions, and an increased incidence of sperm morphologic abnormalities.

The semen quality of most sexually rested stallions stabilizes after three to six ejaculations over a period of 3 to 7 days. If the stallion's semen quality has not stabilized, the practitioner may reach erroneous conclusions concerning the longevity of sperm motility in a shipped,

cooled semen program, the acceptability of different semen extenders or antibiotics that are added to the extender, or the number of mares that may be bred using a single ejaculate.

The goals of the breeding soundness evaluation before the onset of the breeding season are to determine any limitations on the size of the stallion's book; to identify any physical ailments that may have become apparent since the last breeding season; and to determine the suitability of the particular stallion for use in an on-farm or shipped, cooled semen breeding program. Selection of a good quality semen extender to maintain sperm motility for 24 to 72 hours or longer and control pathogenic bacteria in semen is made at this time. Semen quality and bacterial status of extended semen are evaluated periodically throughout the breeding season, in case adjustments are necessary. A final goal of the breeding soundness evaluation should be to establish the presence or absence of pathogens in equine semen, such as EAV, contagious equine metritis (CEM; *Taylorella equigenitalis*), *Pseudomonas* sp., *Klebsiella* sp., and *Streptococcus zooepidemicus*.

## SEMEN COLLECTION

The efficient collection of high quality semen is an important component of an AI breeding program. Semen must be collected in a manner that is safe for the stallion, handlers, veterinarian, and mount mare. The goal of the collection process should be to collect all sperm ejaculated by the stallion without damage to the fertilizing capacity of the sperm.

### Semen Collection Area and Safety

Semen should be collected in a spacious, dust-free, clean environment. The area should be free of distracting noises, animals, equipment, and people. A well-trained, experienced, quiet stallion can be collected safely in a 20-foot square area while mounted on a phantom. However, a stallion of unknown or aggressive breeding behavior requires an area twice these dimensions. Also, if the stallion is to mount an estrous mare for semen collection, a large, safe area is necessary to account for the unexpected movements and reactions of the stallion, mare, and people involved in the collection process.

Loose dirt, shavings, sand, and stone dust should be avoided in the breeding shed because many stallions paw or kick out while in the shed and recontaminate the washed penis.

All individuals involved in the collection of semen should be well informed of the normal collection process and, equally important, the types of adverse situations that can arise during the breeding process. At times, the mount mare may require mild tranquilization. The mount mare always should be restrained with a twitch applied to the nose or with an upper lip chain. Restraint methods need to be in place *before* the mare adversely reacts to being bitten on the hocks, flank areas, or shoulders before or during mating. The use of hobbles should be avoided because of the unpredictable nature of events during live-cover breedings. Additionally, it may be necessary to quickly move the mare away from the semen collection

process. Many breeding sheds require personnel to wear protective headgear and steel-toed shoes. Safety gear worn by handlers and veterinarians should be properly fitted, or the protective function is minimized.

### Semen Collection

Semen usually is collected from the stallion using an artificial vagina (AV). Many types of AVs are available. Each AV model varies slightly in length, diameter, weight, and cost. Descriptions of these AVs are available, in addition to the details of the collection process. A few of the details are pointed out in this chapter. The internal temperature of the AV at the time of usage is usually 44° to 48° C. As the working temperature of the AV drops, the number of mounts per ejaculate rises. Stallions that are reluctant to ejaculate in the artificial vagina, or that have a high number of intromissions per ejaculate, may readily ejaculate on first or second mounts when the internal temperature is elevated to 48° to 50° C. However, an effort should be made to have the horse ejaculate directly into the semen receptacle or coned (nonheated) portion of the AV to avoid heat shock to sperm. Sperm cells exposed to elevated temperatures for as little as 10 to 20 seconds exhibit a circling type motility, have reduced sperm longevity in raw and extended semen, and may be rendered infertile. This same phenomenon may be observed in sperm collected from stallions that ejaculate midway along the length of the AV liner, and water pressure in the AV has to be released before semen can reach the semen receptacle.

Sterile, plastic disposable liners have become available commercially for most types of AVs. The purpose of these disposable liners is to reduce the risk of chemical residue exposure of the semen from the AV liner cleaning process. Additionally, the disposable liner allows the use of the same AV by multiple stallions. However, many stallions object to these liners, and the number of mounts per ejaculation increases. Breakage of the plastic liner may occur during thrusting, and complete inversion of the liner may occur during dismount. If stallions ejaculate on first entry into an AV fitted with a disposable liner, the bacterial contamination of semen is sharply reduced. However, as the number of entries into the AV or the number of thrusts in the AV increases, the bacterial contamination of semen also increases dramatically.

Most AVs can be fitted with a polyester or nylon filter so that gel and debris are filtered at the time of ejaculation. Some of these filters trap considerable seminal fluid and sperm. This may be an important consideration in stallions that produce low numbers of sperm or a low volume of gel-free semen. In these cases, the semen may be filtered after the initial addition of seminal extender.

The AV should be cleaned immediately after use. The AV should be rinsed with volumes of hot water, and dirt, debris, and smegma should be wiped from it. If disposable liners are not used, the rubber liners should be immersed in 70% alcohol for at least 1 hour and hung in a dust-free, dry environment. Soaps and disinfectants should not be used on the rubber equipment to avoid accumulation of chemical residue by the rubber. Without the use of dis-

posable AV liners or thorough cleansing of the AV and its liners, the AV may become contaminated by *Pseudomonas* or *Klebsiella* organisms, *Escherichia coli*, *Taylorella equigenitalis*, or other harmful bacteria and in turn contaminate subsequent semen samples and inoculate the penile surface of the stallion. For these reasons, many farms maintain an individual AV for each stallion.

### Ground Collection of Semen

The collection of semen from stallions while they remain standing on the ground has become commonplace at some breeding farms. With minimal training, many stallions readily accept this method of semen collection. This method of collection may be preferred in horses with laminitis, tarsitis, or hind limb weakness. Additionally, ground collection of semen may be preferred at smaller farms with limited access to mount mares, limited facilities, and lack of adequate horse handlers necessary for other methods of semen collection.

The stallion is brought to the breeding shed or barn aisle that is free of equipment, or he is left in his stall. The stallion is exposed to an estrous or nonestrous mare or to a gelding sufficient to cause the stallion to achieve an erection. The "tease" animal may be free in a stall or 5 to 10 meters away, being held on a lead shank. The stallion's penis is washed with clear, very warm water. With the stallion positioned against a smooth wall to prevent lateral movement, or with him in front of a solid wall to prevent his forward movement, the warm, lubricated AV is placed on the horse's erect penis. The stallion is encouraged to search and thrust into the AV. Once the stallion has engaged in the AV, the collection person's right hand is used to stimulate additional urethral pulsations while the AV is held against the stallion's abdomen with the left hand. The stallion handler may help support the stallion by pushing against the stallion's shoulder with the right hand. For safety, the person collecting semen from the standing stallion should maintain shoulder contact with the stallion.

Stallions may stand on their hind legs while ejaculating, walk slowly forward while ejaculating, or continue to stand with all four feet on the ground. The handler should not discourage the horse from walking forward or standing up. Once horses are trained in the procedure, they usually stand flat-footed with arched back and a head-down posture. At first application of the AV to the standing stallion, a few stallions may kick out or want to nip or bite at the handler. The veterinarian should inform the stallion handler and mare handlers of how the process works and of the likely responses by the stallion before the initiation of this method of semen collection. After a successful collection, the procedure should be repeated in 1 to 2 days, preferably in the same location with the same handler and collection person.

Semen collection with the stallion remaining on the ground has become routine at many farms. This method of collection also has been useful in stallions reluctant to approach an estrous mare or phantom. Aggressive stallions or those that refuse to remain mounted on a phantom are good candidates for ground collection of semen.



## MANAGEMENT OF BREEDING-RELATED PROBLEMS USING SEMEN COLLECTION AND ARTIFICIAL INSEMINATION

A number of medical conditions that are associated with infertility can be diagnosed, treated, and managed using semen collection and AI.

### Hemospermia

The condition known as *hemospermia* refers to the presence of red blood cells in the ejaculate of a stallion. The presence of blood may be noted during dismount after natural service. However, the source of the blood may be unknown. During inspection of the penis and semen collection in an artificial vagina, the source of the blood usually can be determined. If no blood is observed during semen collection, further efforts should be directed toward the mare's reproductive tract.

The amount of blood in an ejaculate may vary from minimal to copious amounts. The blood usually represents fresh bleeding. However, degenerate blood components also have been observed and are brown and frequently clotted. This brown coloration suggests a chronic, healed injury to the urethra or internal genitalia or current inflammation of the vesicular glands.

In most cases, stallions with hemospermia bleed into the ejaculate at the end of the ejaculatory process even in cases in which the distal urethra is the source of bleeding. Affected stallions can continue to be used for breeding by fractionating the semen during collection. During fractionation the first two or three jets of sperm-rich semen are collected in one receptacle, and the remainder is discarded. The Missouri model AV is probably the handiest for the fractioning of semen because the semen receptacle can be readily changed during ejaculation, and minimal mixing of seminal jets occurs from ejaculation until entry into the various vessels.

An open-ended AV (Polish model) also may be used to collect individual jets of semen. An open-ended AV can be made by shortening the Lane or Colorado model artificial vagina to a total length of 40 cm. Only the water jacket liner is used. The Missouri model AV can be modified by removal of the coned portion of the AV, leaving only the water jacket. During ejaculation, the enlarged glans penis of the stallion is at the end of the AV so that the urethra can be visualized. An assistant can "catch" the individual jets of semen using a large-mouthed funnel and attached collection bag.

The source of bleeding is usually the distal urethra. The mucosa of the distal urethra may have been traumatized or affected by habronemiasis. Fibropapilloma of the external penile surface also may be a source of blood in semen. Urethroscopy may be necessary to investigate urethral mucosal injuries or conditions of the internal genitalia. The stallion may need to be sexually rested to hasten healing, dependent on the site and severity of any lesions.

### Presence of Urine in Semen

The presence of urine in an ejaculate during live-cover matings usually goes unnoticed. The frequency and amount of urine contamination of semen is variable in any given af-

ected stallion. The contamination of semen with urine results in reduced fertility, reduced sperm motility and longevity of motility, and uterine inflammation. The cause of urine contamination of semen is usually unknown but may be associated with equine herpesvirus infection (EHV), equine protozoal myelitis (EPM), cystitis, or tumors. This condition usually is diagnosed by collection of semen in an AV. Affected stallions may not contaminate every ejaculate of semen. The presence of urine in an ejaculate can be documented by color, odor, creatinine, and urea nitrogen concentrations in semen. In most cases, the urine is emitted near the end of the ejaculatory process.

Treatment of stallions with a clinical history of sporadic or repeated urine contamination of their ejaculates should be aimed at correction of the above conditions, if they are diagnosed. Breeding managers may encourage a stallion to urinate before semen collection by exposing the stallion to the feces of another stallion or mare or by placing the horse in a freshly bedded stall. This may reduce the incidence of urospermia but is unlikely to eliminate it. Because most affected stallions emit urine near the end of ejaculation, fractionation of seminal ejaculates or use of an open-ended Polish-style AV may allow the successful use of the stallion in an AI program. The osmotic pressure of urine is very high, so immediately extending semen or allowing the stallion to ejaculate into semen extender may reduce the damaging effect of urine contamination on sperm motility. However, the effect of this procedure on fertility is unknown but will likely be dependent on the amount of urine present in semen. Limited evidence exists of controlling urospermia by oral treatment of the stallion with 200 to 500 mg of imipramine hydrochloride daily.

### Bacterial Contamination of Semen

Semen may become heavily contaminated with bacteria of all types from the surface of the stallion's penis, AV, water used for washing, and environment. Excessive washing of the stallion's penis and the use of soaps or disinfectants on the stallion's penis may alter the penile skin and allow overgrowth of certain bacteria, such as *Pseudomonas* sp., *Klebsiella* sp., and *E. coli*. In these cases, white blood cells are not present in the ejaculate. The presence of these bacteria in a shipped, cooled semen sample has minimal effect on sperm viability. However, the addition of certain antibiotics to control these organisms in extended, fresh or frozen semen, such as gentamicin or polymixin B, may adversely affect motility and fertility. Insemination of mares with heavily contaminated semen may result in pregnancy, increased incidence of early embryonic mortality, postbreeding uterine fluid accumulation, or persistent endometritis. Use of systemic antibiotics to control penile surface bacteria is not effective. Systemic antibiotics used in stallions with internal bacterial infections of the reproductive tract are also rarely effective.

The source of excessive contamination of the semen should be determined through culturing multiple sites of the prewash and postwash penis, preejaculate and post-ejaculate urethral swabbing, raw semen, and the artificial vagina before use. In this manner, specific corrective measures can be instituted.

Bacterial contamination of semen increases dramatically with prolonged thrusting by the stallion and repeated entries into the AV. If a stallion readily accepts the use of disposable, plastic liners to the AV, their use eliminates the artificial vagina as a source of contamination. Management should focus on reduction of multiple mounts per ejaculation by proper preparation of personnel, the mount mare, AV, and the stallion.

The collection of semen using an open-ended AV results in virtually bacteria-free raw semen samples. In an AI program, dilution, use of an open-ended AV, cooling, and the addition of suitable antibiotics to the extender reduces bacterial numbers in fresh and frozen semen, but penile washing and the freezing process have minimal or no effect.

### Abnormal Seminal Plasma

The seminal plasma of stallion ejaculates rarely is evaluated. However, a limited number of stallions are suspected of having abnormal seminal plasma, based on initial motility and longevity of sperm motility. The specific characteristics of abnormal seminal plasma have not been identified. Most of these stallions have ejaculates characterized by low sperm numbers, low sperm concentration, normal sperm morphology, poor longevity of motility in semen extenders, and a large disparity between total and progressive sperm motility estimates. These stallions have poor fertility under typical AI programs. Fertility can be improved in these stallions by immediate extension of the raw semen in a skim milk-glucose extender, followed by centrifugation to produce a soft pellet in the centrifuge tube. The supernatant fluid is aspirated or decanted from the samples. The sperm pellet is then resuspended in a skim milk-glucose extender. No more than 20% of the initial seminal plasma remains in the extended semen sample. The centrifugation process results in 70% to 80% of the sperm remaining in the soft pellet. If maximal harvest of sperm is required because of low sperm numbers per ejaculate in these stallions, the supernatant fluid can be centrifuged a second time without detriment to the sperm.

### Sperm Stasis or 'Plugged Ampullae'

The clinical signs presented by a stallion with sperm stasis of the ampullae include a history of normal fertility followed by a period of extended sexual rest and subsequent sterility with absence of sperm in the ejaculate. Affected stallions are frequently middle-aged and good sperm producers. The condition usually affects both ampullae but also may be unilateral. During semen collection of stallions with sperm stasis, an increased frequency of mounts per ejaculate occurs, and initial ejaculates may be devoid of sperm, have no or very low sperm motility, and frequently contain a high percentage of sperm with detached heads. With repeated, frequent semen collections, seminal parameters improve and return to normal for the particular stallion. Relief of complete, bilateral blockage of the ampullae may require a few to more than 20 ejaculations by the stallion.

Semen collections should be made repeatedly over a short span of time to help clear the ampullae. The stallion's libido should be used as a guide to semen collection frequency. Many of these stallions can be collected five or more times per day. Prolonged teasing of the stallion before semen collection and manual massage of the ampullae, per rectum, may hasten dislodgement of the inspissated sperm in the crypts of the ampullae. The systemic administration of 10 to 20 IU oxytocin may be helpful in some cases. Sperm stasis may recur in a stallion after prolonged rest.

### Low Numbers of Sperm per Ejaculate

A stallion may have low sperm output for a variety of reasons, including overuse, small testicular size, and testicular degeneration. In a cooled, shipped semen-breeding program, problems arise if the total number of sperm per ejaculate is low (less than  $1.5 \times 10^9$  sperm), or if sperm concentration is low ( $<75 \times 10^6$  sperm/ml). If total sperm output is low, it may not be feasible to breed more than a single mare per ejaculate, because  $500 \times 10^6$  morphologically normal or progressively motile sperm are recommended for reasonable fertility with transported semen. Stallions with low sperm output frequently have a high incidence of abnormal sperm and reduced motility. Shipment of semen to a single mare on consecutive days, or using air transport for same-day collection and insemination may compensate for these semen deficiencies. A limited semen collection schedule for the stallion also may be an option.

Semen with low sperm concentration is problematic, because dilution of raw semen to maximize sperm longevity may require a dilution ratio of 1:3 or even 1:5. A limited volume of extended semen can be shipped in the transport container. Therefore too few sperm may be shipped to the mare to expect high fertility. Low sperm concentration may be characteristic of the ejaculates of some stallions and is commonly observed in the ejaculates of draft horse stallions. Ejaculates of low sperm concentration should be diluted in an acceptable extender, such as nonfat, dry skim milk-glucose based extender, at a dilution rate of 1:1. The extended semen is then centrifuged in sterile, chemical-free glassware or plastic to produce a "soft" pellet of sperm. A frequently used protocol is to centrifuge the extended semen at  $300$  to  $500 \times g$  for 10 to 15 minutes. The supernatant is decanted to leave 10% to 20% seminal plasma. The centrifuged semen then is extended to an appropriate volume for cooling and transport. An alternative to the centrifugation of semen may be the collection of only the sperm-rich fractions of semen, using an open-ended artificial vagina, as previously described.

### Supplemental Readings

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- Hurtgen JP: Semen collection in stallions. In Samper JC (ed): Equine Breeding Management and Artificial Insemination, Philadelphia, WB Saunders, 2000.

## CHAPTER 5.13

# Endocrine Diagnostics for Stallion Subfertility

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### THE HYPOTHALAMIC-PITUITARY-TESTICULAR AXIS

In many mammalian species, including the stallion, normal spermatogenesis depends on a functional hypothalamic-pituitary-testicular (HPT) axis that involves classic feedback mechanisms. An excellent review by Amann on the physiology and endocrinology of reproductive function in the stallion describes the involvement of the HPT in spermatogenesis. Roser and colleagues presented additional endocrine data regarding the action of the reproductive hormones within the HPT axis of the stallion (Figure 5.13-1). Briefly, gonadotropin-releasing hormone (GnRH) from the hypothalamus stimulates the production and secretion of pituitary luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which in turn signals the testis to produce and secrete important hormones such as testosterone (T), estrogen, and inhibin for spermatogenesis. The testicular hormones apparently have either a negative or positive feedback effect on the hypothalamus and/or pituitary. Recent evidence suggests that T acts mainly at the level of the hypothalamus to inhibit GnRH. Estrogen acts at the level of the pituitary to enhance the action of GnRH in the production and release of LH. Most likely inhibin is the major hormone to inhibit the release of FSH. Whether T and/or estrogen have a role in regulating FSH at the level of the pituitary is unclear. Estrogen's role in regulating GnRH at the level of the hypothalamus is also uncertain.

In addition, paracrine/autocrine factors may be involved in modulating the actions of the reproductive hormones on testicular function. The paracrine/autocrine system, a relatively newly discovered system, apparently is involved in carrying out local events. Paracrine factors are secreted from one cell in the testis and act on different cell types in the testis. Autocrine factors are secreted from one cell in the testis and have actions on their own cell type.

These factors are now recognized as important modulators of reproductive events in many mammalian species. They include testosterone, estrogen, inhibin, growth factors, transferrin, cytokines, and many others. Recent evidence in this author's laboratory suggests that idiopathic subfertility may be due to a testicular dysfunction associated with a decline in paracrine/autocrine factors (Figure 5.13-2). Except for GnRH and some of the paracrine/autocrine factors, the reproductive hormones can be measured in the peripheral circulation for diagnostic purposes. Unfortunately, a true measurement of the paracrine/au-

tocrine factors within the testes can be made only by analysis of testicular tissue via a testicular biopsy. Recent work by Faber and Roser suggests that testicular biopsies can be performed without apparent detrimental effects but, in general, the procedure is not without risk.

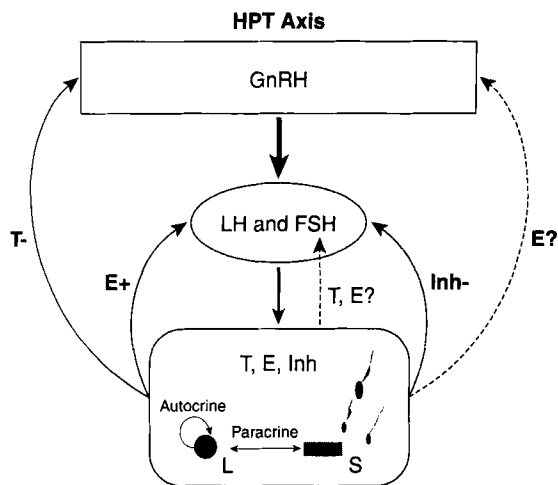
### STALLION SUBFERTILITY AND ENDOCRINE PARAMETERS

Subfertility can be defined in terms of pregnancy rates per cycle (<20% to 30% per cycle; normal >50% per cycle) or pregnancy rates per season (<60% per season; normal >80% per season). It can be associated with changes in sperm numbers and/or motility, changes in the texture of the testes, and/or testicular degeneration. Certainly a number of problems can affect stallion fertility that have nothing to do with the endocrine system such as hematospermia, urospermia, venereal diseases, neoplasms, and viral and bacterial infections. Endocrine diagnostics may not be useful in these cases. They can be useful in cases of idiopathic subfertility or testicular degeneration, particularly for identifying the location of the problem. A change in the normal endocrine parameters does not necessarily mean that the problem is endocrine in nature. It may be the result of a primary nonendocrine type of dysfunction.

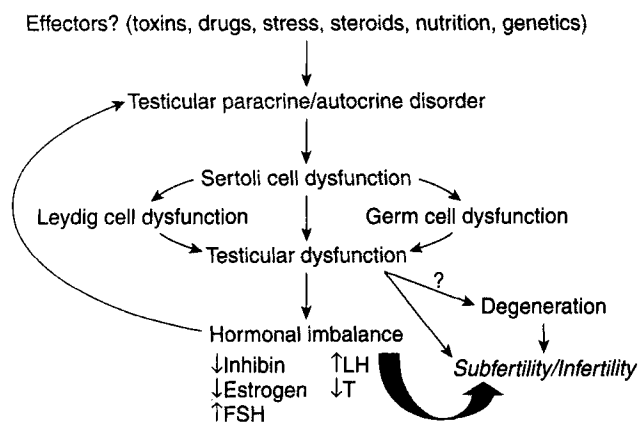
### DIAGNOSTIC EVALUATION OF THE HPT AXIS

When taking blood samples for measurement of reproductive hormones, the clinician should keep in mind the following concepts:

- Secretion of hormones can be episodic throughout the day, so taking more than one blood sample to get an average baseline is important. Six are recommended, once every hour on the same day between 10 AM and 3 PM. Alternatively, if only a rough estimate of baseline values is needed, a simpler approach is to take three blood samples, one each day for 3 days at the same time each day.
- Baseline concentrations of hormones can increase and decrease during the day with some hormones, such as testosterone, reaching its highest levels during the middle of the day. Consistency is important in taking blood samples at a certain time of day for comparative purposes. The time of day is not as



**Figure 5.13-1** Hypothalamic-pituitary-testicular (HPT) axis of the stallion. *GnRH*, Gonadotropin-releasing hormone; *LH*, luteinizing hormone; *FSH*, follicle-stimulating hormone; *T*, testosterone; *E*, estradiol; *Inh*, inhibin; *L*, Leydig cell; *S*, Sertoli cell.



**Figure 5.13-2** Hypothesis of events that may occur after an initial decline in paracrine/autocrine testicular factors as a result of effectors such as toxins, drugs, stress, steroids, and nutritional or genetic abnormalities. *FSH*, Follicle-stimulating hormone; *LH*, luteinizing hormone; *T*, testosterone. (Modified from Roser JF: Endocrine basis for testicular function in the stallion. *Theriogenology* 1997; 48:883-892.)

important as is the adherence to that time of day when taking multiple samples from the same animal or different animals.

- Concentrations among fertile stallions vary. The concentrations should be within a normal range. The normal range can be different from laboratory to laboratory because of the use of different reagents and different assays used to run the samples. Each laboratory should provide its own values for the normal range.
- A seasonal variation exists: Highest levels of hormones are found during the breeding season (March through September) and lowest during the non-breeding season (October through February).
- Either plasma or serum samples can be used to evaluate endocrine parameters.

- Usually a 10-ml blood sample is adequate for the measurement of circulating levels of LH, FSH, T, estradiol, and inhibin.

## DIAGNOSTIC MEASUREMENT OF ENDOCRINE, PARACRINE, AND AUTOCRINE FACTORS

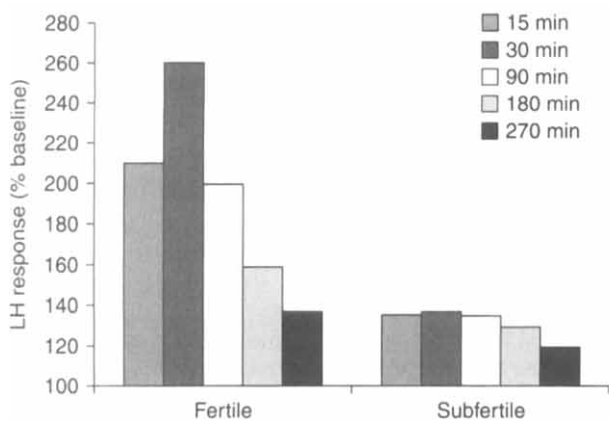
### Serum or Plasma Concentrations of Luteinizing Hormone, Follicle-Stimulating Hormone, Estradiol, Inhibin, and Testosterone

To obtain accurate baseline levels, 10 ml of venous blood is taken from the jugular once every hour from 10 AM to 3 PM on the same day. A less accurate measurement that is still useful and easier to obtain is to take 10 ml of venous blood every day for 3 days between 9 and 10 AM. Blood samples are kept at 4° C until processed. Plasma or serum is removed within a couple of hours and stored at -20° C until analyzed. Data from the six hourly samples provide information relative to the occurrence of a midday rise in testosterone. A similar LH pattern should be observed. The association of LH and T rising at the same time indicates that LH is appropriately stimulating the testes to produce T. A subfertile stallion with testicular problems may show a rise in LH without a corresponding rise in T. In general, based on previous research, a stallion with declining fertility usually shows changes in hormone levels in the following order: (1) increasing levels of FSH, (2) decreasing levels of estradiol and inhibin, (3) decreasing levels of LH and finally when the stallion is infertile, (4) decreasing levels of testosterone. These changes may take a few months or a few years depending on the disorder. If the hourly blood-sampling regime is not practical, the three daily blood sample regime can be used to adequately assess subfertility.

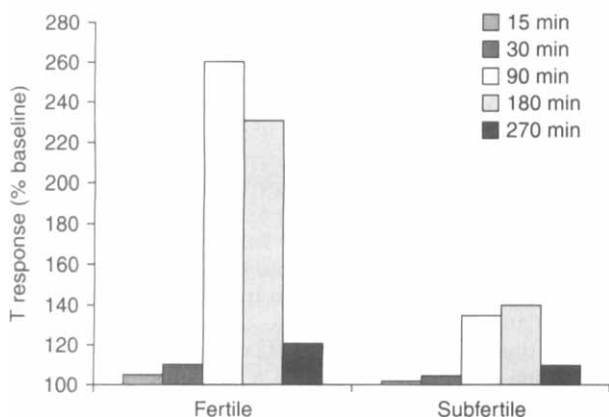
### Single-Pulse Gonadotropin-Releasing Hormone Challenge Test

To assess pituitary and testicular responsiveness, a single dose of 25 µg of GnRH (Cystorelin, Merial) is given intravenously (IV) at 9 AM. Blood samples are collected at 30 minutes before, at the time of injection, and every 30 minutes thereafter up to 120 minutes. Blood samples are kept at 4° C until processed. Plasma or serum is removed within a couple of hours and stored at -20° C until analyzed for LH and T.

An abnormal response to a single challenge may help in the diagnosis of a hypothalamic-pituitary disorder and/or a testicular disorder as seen in Figures 5.13-3 and 5.13-4. The subfertile stallions in these figures appear to have a low pituitary and testicular response, suggesting either a primary pituitary or testicular disorder. A challenge with human chorionic gonadotropin (hCG) would be the next step to determine whether it is a primary testicular disorder (see discussion of hCG challenge). In other cases, measurement of plasma hormone levels in addition to a GnRH challenge can be revealing. For example, the stallion with low baseline levels of LH but good responsiveness to exogenous GnRH may have a problem at the hypothalamus, that is, he cannot produce or secrete nor-



**Figure 5.13-3** Temporal changes in mean luteinizing hormone (LH) responses, expressed in terms of percent baseline, to intravenous (IV) injection of 25 µg of exogenous gonadotropin-releasing hormone (GnRH) in fertile and subfertile stallions. (Modified from Roser JF, Hughes JP: Dose-response effects of GnRH on gonadotropins and testicular steroids in fertile and subfertile stallions. *J Androl* 1992b; 13:543-550.)

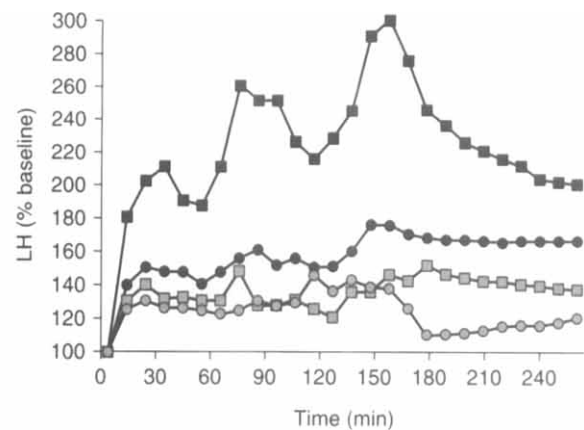


**Figure 5.13-4** Temporal changes in mean testosterone (T) responses, expressed in terms of percent baseline, to intravenous (IV) injection of 25 µg of exogenous gonadotropin-releasing hormone (GnRH) in fertile and subfertile stallions. (Modified from Roser JF, Hughes JP: Dose-response effects of GnRH on gonadotropins and testicular steroids in fertile and subfertile stallions. *J Androl* 1992b; 13:543-550.)

mal levels of GnRH. This syndrome is referred to as *hypogonadotropic hypogonadism*.

### Three-Pulse Gonadotropin-Releasing Hormone Challenge Test

To assess pituitary responsiveness to endogenous GnRH, a series of small challenges using exogenous GnRH is needed. This test also can be helpful in evaluating testicular output. Three small IV doses (5 µg/dose) of GnRH (Cystorelin, Merial) are given 1 hour apart in the non-breeding season starting at 9 AM. The LH response from baseline is more pronounced in the non-breeding season when HPT axis activity is at its lowest. Blood samples are taken every 10 minutes throughout the test, beginning 30 minutes before the first injection. The entire process takes 210 minutes. Blood samples are kept at 4° C until processed. Plasma or serum is re-



**Figure 5.13-5** Temporal changes in luteinizing hormone (LH) response in fertile (dark symbols) and subfertile (light symbols) stallions during the breeding (squares) and non-breeding (circles) seasons. Responses are expressed in terms of percent baseline levels, to three challenges of exogenous gonadotropin-releasing hormone (GnRH; 5 µg) given intravenously at 0, 60 and 120 minutes. (Modified from Roser JF, Hughes JP: Seasonal effects on seminal quality, plasma hormone concentrations and GnRH-induced LH response in fertile and subfertile stallions. *J Androl* 1992a; 13:214-223.)

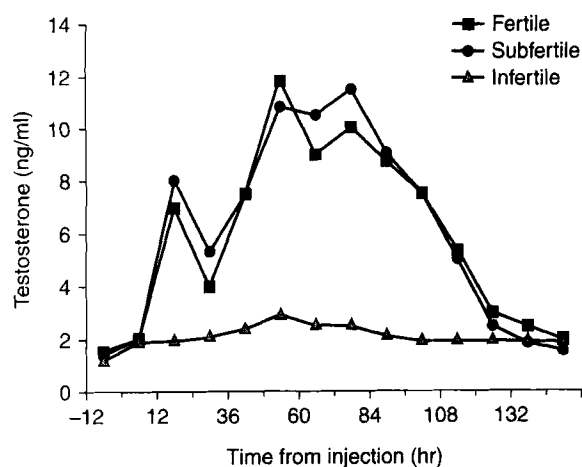
moved within a couple of hours and stored at -20° C until analyzed for LH. This test evaluates specifically the pituitary for its ability to be primed with a series of GnRH pulses. It also evaluates the testis for its ability to provide the necessary factors for the priming effect to occur like estrogens. A normal priming effect is observed when LH is released at a consistently higher level after each challenge. Compared with fertile stallions, subfertile stallions have a significantly lower response to the second and third injection of GnRH in the nonbreeding season (Figure 5.13-5).

### Challenge with Human Chorionic Gonadotropin

To assess testicular responsiveness, a single dose of hCG (10,000 IU: Chorulon; Intervet, Millsboro, Del.) is given IV at 9 AM. Blood samples are collected at 0 and 30 minutes and at 1, 2, 4, 6, 12, and 60 hours. A biphasic response occurs, with the first peak observed by 12 hours and the second peak by 60 hours (Figure 5.13-6). A twofold to fourfold increase should be observed by 3 hours in most normal stallions. Blood samples are kept at 4° C until processed. Plasma or serum is removed within a couple of hours and stored at -20° C until analyzed for T. Because treating with hCG directly stimulates the testis a poor T response along with normal levels of LH and low levels of circulating testosterone suggest the problem is at the level of the testes. A study on fertile, subfertile, and infertile stallions indicated that only the infertile stallions had a poor testicular response to hCG (see Figure 5.13-6). A lower dose of hCG (2500-5000 IU) may be more helpful in identifying subfertile stallions.

### Testicular Biopsy

Testicular biopsy provides a direct measurement of endocrine, paracrine, and autocrine factors in testicular



**Figure 5.13-6** Temporal changes in mean plasma concentrations of testosterone before and after a challenge of hCG (human chorionic gonadotropin; 10,000 IU) or saline given intravenously at time 0 in fertile, subfertile, and infertile stallions. (Modified from Roser JF: Endocrine profiles in fertile, subfertile and infertile stallions: testicular response to hCG in infertile stallions. *Biol Reprod Mono* 1995; 1:661-669.)

tissue and should be done under sterile conditions. To obtain three biopsy punches using a spring-loaded biopsy instrument (Bard Inc., Covington, Georgia) attached to a 14-gauge split needle, the stallion is secured in a stanchion and sedated with a combination such as detomidine hydrochloride (Dormosedan) and butorphanol tartrate (Torbugesic). The scrotum is prepared aseptically with iodine scrub and local anesthesia is induced subcutaneously with approximately 1 ml of a 2% (v/v) solution of lidocaine hydrochloride. A small incision is made in the scrotum in the center of the cranio-lateral quarter of the most affected testis. The testis is held down in the scrotum. The sterile

14-gauge split needle coupled to the spring loaded biopsy instrument is placed through the incision against the tunica vaginalis, subsequently fired with the needle projecting into the testicular parenchyma, and then removed.

Two subsequent samples are collected through the same incision but at slightly different angles. Two punches are each placed in 1.2 ml of phosphate buffered saline and snap frozen in dry ice and alcohol or liquid nitrogen and stored frozen at  $-70^{\circ}\text{C}$  until processed for endocrine/paracrine/autocrine factors. The third sample is placed in Bouin's solution for 6 hours, transferred to 50% alcohol, and submitted for histological examination. A recent study investigating levels of testicular hormones in fertile, subfertile, and infertile stallions suggests inhibin levels in testicular extracts may be an early marker for declining fertility.

### Supplemental Readings

- Amann RP: Anatomy, physiology and endocrinology. In McKinnon AO, Voss JL (eds): *Equine Reproduction*, pp 658-685, Philadelphia, Lea & Febiger, 1993.
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## CHAPTER 5.14

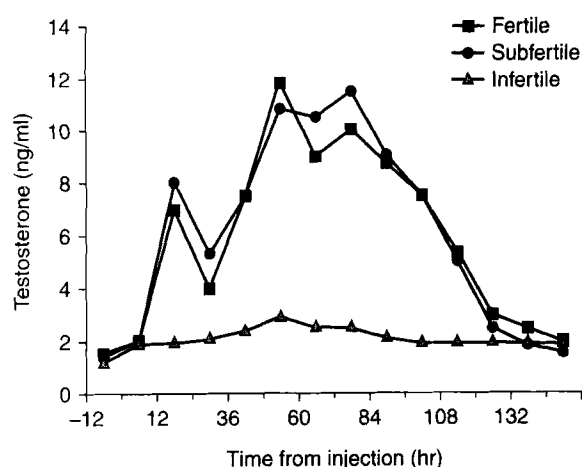
# Evaluation of the Equine Ovary

GRANT S. FRAZER  
Columbus, Ohio

### THE NORMAL OVARY

The equine ovary has a characteristic kidney-bean shape. The depression on the ventral border is the site of the ovulation fossa. Unlike many species, the follicle does not rupture through the surface of the mare's ovary. Instead, all ovulating follicles "point" towards the ovulation fossa and all ovulations occur through this site on the ovary. Another chapter in this section describes evaluation of the

cyclic equine ovary by palpation per rectum and ultrasonographic imaging (see Chapter 5.8: "Use of Ultrasound to Stage Estrus and Predict Ovulation"); the purpose of this chapter is to review the various abnormalities that clinicians may detect during routine palpation of an equine ovary. Evaluation of an equine ovary requires consideration of the time of the year, age, and the pregnancy status of the mare.



**Figure 5.13-6** Temporal changes in mean plasma concentrations of testosterone before and after a challenge of hCG (human chorionic gonadotropin; 10,000 IU) or saline given intravenously at time 0 in fertile, subfertile, and infertile stallions. (Modified from Roser JF: Endocrine profiles in fertile, subfertile and infertile stallions: testicular response to hCG in infertile stallions. *Biol Reprod Mono* 1995; 1:661-669.)

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## CHAPTER 5.14

# Evaluation of the Equine Ovary

GRANT S. FRAZER  
Columbus, Ohio

### THE NORMAL OVARY

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cyclic equine ovary by palpation per rectum and ultrasonographic imaging (see Chapter 5.8: "Use of Ultrasound to Stage Estrus and Predict Ovulation"); the purpose of this chapter is to review the various abnormalities that clinicians may detect during routine palpation of an equine ovary. Evaluation of an equine ovary requires consideration of the time of the year, age, and the pregnancy status of the mare.

## SMALL, INACTIVE OVARIES

### Physiologic Conditions

Ovarian senescence can occur in aged mares, with lengthening of the follicular phase occurring despite the presence of elevated levels of gonadotropins. This may be due to a reduction in the number of primordial follicles that are available for recruitment. Abnormal pituitary function (Cushing's disease) also should be considered in aged mares.

### Effects of Anabolic Steroids

Administration of anabolic steroids to performance animals can have detrimental effects on future fertility, and should be avoided. The presence of clitoral hypertrophy may suggest that a filly has been medicated with anabolic steroids. Low doses can cause aggressive or stallion-like behavior. Higher doses may inhibit ovarian activity by preventing follicular development and ovulation.

### Chromosomal Abnormalities

Evaluation of the karyotype should be considered when a mare of breeding age is determined to have gonadal hypoplasia. The domestic horse (*Equus caballus*) has 62 autosomes and two sex chromosomes. Therefore the normal chromosome number for a mare is 64,XX. Absence of a sex chromosome (63,X gonadal dysgenesis) is the most common chromosomal abnormality in the mare. This XO condition is analogous to Turner's syndrome in humans. A mare that is small for her age and has small, inactive ovaries is likely to have this condition. The external genitalia tend to be small, and the tubular tract is small and flaccid. A variation of this condition occurs when a mare has a mosaic or chimeric karyotype (63,XO/64,XX).

## ENLARGED OVARIES

### Anovulatory Follicles

Large, anovulatory follicles are a normal finding during the spring and fall transition periods. Anovulatory follicles can exceed 10 cm in diameter and may persist for several weeks. The cause is likely to be abnormal estrogen production by the follicle and/or insufficient release of pituitary gonadotropin to induce ovulation. Often the ultrasonographic image reveals scattered free-floating echogenic spots as a result of the presence of blood in the follicular fluid (hemorrhagic follicles). In others are echogenic fibrous bands resulting from gelatinization of the hemorrhagic fluid. Although human chorionic gonadotropin (2500 IU IV) or a GnRH implant may induce ovulation, in most cases the treatment is ineffective. Fortunately most of these anovulatory follicles spontaneously regress within 1 to 4 weeks. Breeding a mare in anticipation of ovulation of a persistent follicle is unwise because fertility of the aged oocyte is likely to be poor.

Clinicians should be aware that not all palpable and ultrasonographically imaged structures around the ovary have to be follicles. Fossa cysts and parovarian (fimbrial) cysts can be found in many mares as an incidental finding.

These structures tend to arise from remnants of the embryonic (mullerian and wolffian) duct systems. If they are of a significant size they should be noted on the mare's breeding records, but they generally are not associated with any reduction in fertility. Theoretically an excessively large cyst could interfere with ovulation or oocyte transport.

### Hematoma

During the physiologic breeding season in a healthy, non-pregnant mare, a surge of luteinizing hormone from the anterior pituitary results in rupture of the mature follicle (ovulation). Normally some hemorrhage from blood vessels in the theca layer occurs, and this results in a soft, intermediate structure—the corpus hemorrhagicum. Immediately after ovulation a depression may be palpable, but this is soon replaced by the developing corpus luteum. The theca cells and invading granulosa cells become luteinized such that the serum progesterone level is elevated until endometrial prostaglandin brings about luteolysis.

A hematoma is the most likely explanation for a unilateral ovarian enlargement during the physiologic breeding season. Excessive postovulatory hemorrhage is not uncommon. The former follicle can become distended markedly. Treatment is not indicated because the structure is essentially an abnormally large corpus hemorrhagicum. Behavior will be normal. The mare continues to have regular estrous cycles, and the opposite ovary remains functional. Serum hormone levels are normal. The hematoma resolves over a period of several weeks, and normal ovarian function can be expected to return in most cases.

### Pregnancy

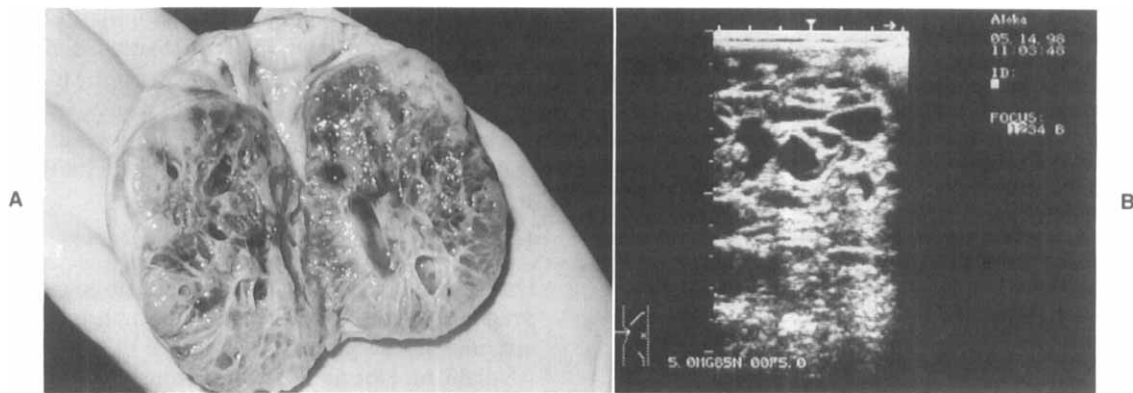
Although an ovarian tumor could begin development during pregnancy, the most likely explanation for ovarian enlargement and abnormal behavior during this time is normal physiologic events. Secondary corpora lutea tend to cause bilateral ovarian enlargement after approximately day 40 of gestation. Expressions of estrus and stallion-like or just aggressive behavior can occur during pregnancy. The large fetal gonads are a significant source of testosterone. Obviously progesterone from the corpora lutea and progestins from the placenta are present. By 2 to 3 months of gestation, testosterone levels can exceed 100 pg/ml and then continue to rise until about 6½ months. The testosterone concentrations then gradually decline to basal levels at parturition.

### Granulosa Cell Tumors

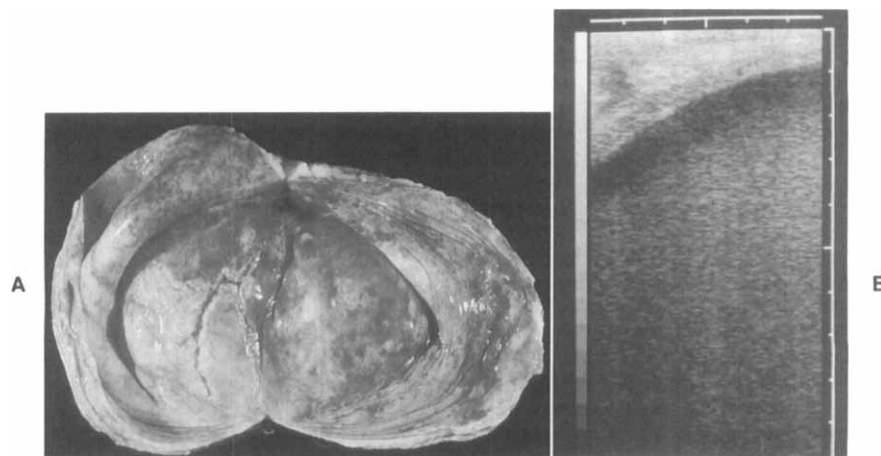
In a normal ovary the granulosa cells line the inside of follicles, whereas the theca cells surround the outside of the follicle. The theca cells produce testosterone. Both the granulosa and theca cells are involved in the steroidogenic pathway that leads to estradiol production. The granulosa cells also produce the protein hormone, inhibin.

The granulosa cell tumor (GCT) is the most common tumor of the equine ovary. These tumors tend to be unilateral, slow growing, and benign. In fact, they can develop during pregnancy. If a GCT is detected at the foal heat, it may be possible to remove the ovary and have the mare bred back later that season. This depends on the

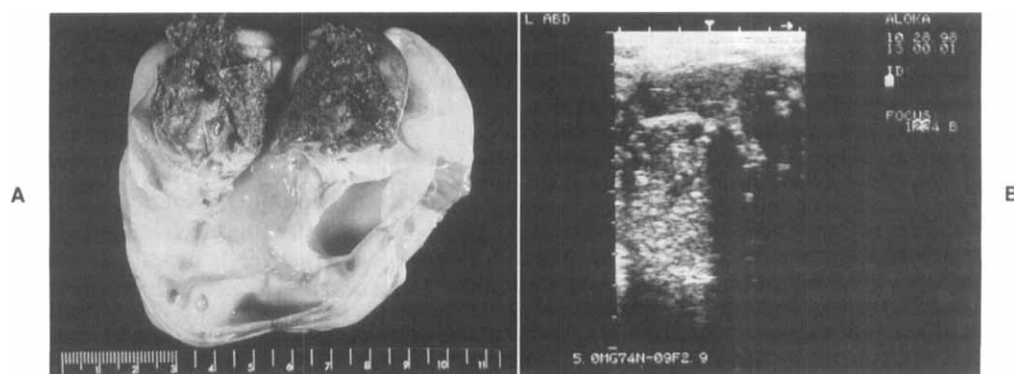




**Figure 5.14-1** **A**, Granulosa cell tumor (GCT). The ovulation fossa is obliterated. The tumor is slow-growing and can vary in size depending on how long it has been present. **B**, The ultrasound image of a GCT is characteristic, with sharp, irregular structures instead of the normal follicular shapes. The honeycomb image varies depending on the density of connective tissue.



**Figure 5.14-2** **A**, A granulosa cell tumor (GCT) can vary from quite dense and solid, through to a large unilocular cystic structure. When opened, these unilocular GCTs collapse. Sections must be submitted from several sites for histopathologic examination because not all of the surrounding tissue confirms the diagnosis. **B**, Ultrasonographic image of a unilocular GCT. Note the thick wall. The bloody fluid is characterized by the presence of free-floating echogenic spots that swirl when the ovary is moved by ballottement.



**Figure 5.14-3** **A**, An ovarian teratoma can contain a mixture of tissues, such as cartilage, bone, hair, and mucus. The surface is often sharp and irregular on palpation. **B**, The ultrasound image of a teratoma varies with the types of tissue contained within. Note the distal acoustic shadowing below aberrant curvilinear tissue (i.e., cartilage and bone) in an ovarian teratoma.

**Table 5.14-1**  
**Hormonal Concentrations in Mares**  
**with a Granulosa Cell Tumor**

Hormone	Diagnostic Level	Incidence
Testosterone	More than 50 to 100 pg/ml	50%-60% of cases
Inhibin	More than 0.7 ng/ml	~90% of cases

time of year that the mare foals and also the degree of follicular suppression present in the contralateral ovary.

Although GCTs are steroidogenically active, the hormonal milieu can vary from case to case. This affects the amount of follicular activity on the contralateral ovary and the type of behavior being exhibited. Typically the opposite ovary is small and inactive, but occasionally a GCT presents on one ovary while a corpus luteum is on the other. Owners may report that the mare has failed to exhibit estrous behavior (prolonged anestrus) or that it is continuously displaying signs of being in estrus (nymphomania). A dangerous side effect in some mares is aggressive behavior towards the handler. These mares tend to exhibit stallion-like behavior and may develop a crested neck and clitoral hypertrophy if the tumor has been present for some time.

Loss of the characteristic kidney-bean shape is usually a good indication that a tumor may be present in a small ovary (Figure 5.14-1, A). Often the ovary is too large to be palpated thoroughly. In both instances the characteristic multicystic (honeycomb) image on an ultrasound examination can support the diagnosis (Figure 5.14-1, B). Occasionally the GCT may present as a large unilocular cyst (Figure 5.14-2).

The ultrasonographic diagnosis can be supported by hormonal assays if necessary (Table 5.14-1). Most GCT appear to secrete sufficient inhibin to suppress pituitary release of follicle-stimulating hormone (FSH), and this probably explains the typical suppression of follicular activity on the contralateral ovary. If a significant theca cell component exists in the tumor then the serum testosterone level is elevated, and these mares are more likely to be aggressive and exhibit stallion-like behavior. Although progesterone levels tend to be low ( $<1$  ng/ml) in affected mares, in some instances cyclic activity may continue in the presence of a GCT.

Indications for removal of these benign tumors include breeding purposes, behavioral problems, and in some cases colic episodes. Diagnosis must be certain because a histopathologic diagnosis of normal ovarian tissue can be difficult to explain to an owner once the ovary has been removed. Veterinarians must explain to owners that not all behavioral problems are ovarian in

origin. An endometrial biopsy and cervical evaluation are recommended if the mare is to be used for breeding purposes. Although the abnormal hormonal environment can cause reversible changes in the density of the endometrial glands, chronic degenerative changes including fibrosis limit the mare's ability to carry a foal to term. The affected ovary can be removed by several surgical approaches, depending on the size of the GCT and the preference of the surgeon. Options for ovariectomy include laparoscopy, colpotomy, and flank and ventral midline laparotomy. The time until subsequent ovulation on the remaining ovary can vary tremendously, and owners should be advised that it might take up to 6 to 8 months.

### Other Ovarian Tumors

Although they are rare, teratomas are the next most common ovarian tumor after a GCT. They are also unilateral but are not hormonally active and do not alter the mare's behavior. The opposite ovary remains active and the mare exhibits normal estrous activity during the physiologic breeding season. A teratoma is a germ cell tumor and may contain cartilage, bone, hair, mucus, and other tissues. The surface of the ovary tends to be sharp and irregular on palpation, and the varying density of the aberrant tissues causes abnormal shadows on the ultrasound image (Figure 5.14-3). Although an ovarian teratoma generally is thought of as being benign, this author has reported on one malignant case that had metastasized to several organs.

Even more rare tumors of the equine ovary include cystadenomas and dysgerminomas. Cystadenomas tend to be benign, whereas dysgerminomas may be malignant. They are both unilateral and hormonally inactive. Thus the contralateral ovary and behavior are normal. The ultrasonographic image of a cystadenoma can resemble that of multiple follicular activity. The same considerations for surgical removal apply as for GCT.

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## CHAPTER 5.15

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# Mare Behavior Problems

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**T**his chapter briefly outlines the four most common complaints concerning reproductive behavior in mares: (1) failure to show estrus or to stand for breeding, (2) maternal behavior problems, (3) stallionlike behavior, and (4) estrus cycle-related performance problems in mares.

### FAILURE TO SHOW ESTRUS OR TO STAND FOR BREEDING

Research and clinical experience consistently indicate that most mares show estrus, or some detectable and reliable change in behavior consistent with estrus, in association with ovulation. A stallion given free access to the mare probably would have no difficulty detecting estrus and proceeding with normal breeding. A trained and careful observer would see changes in response to prolonged interaction with a male. Therefore "failure to show estrus" or "silent ovulation" in most cases represents management failure to adequately elicit and/or detect estrus under farm conditions. Difficulty detecting estrus also is complicated in certain individual mares that may naturally show good estrus for only a few hours.

The recommendation for detection of estrus in mares is teasing for at least 5 minutes, preferably with the mare at liberty to approach the stallion, along a fence line or with the stallion in a teasing pen. This enables a fuller range of mare estrus behavior and avoids submissive behavior evoked by forced encounter with the stallion. Sometimes it helps to tease with two or more stallions (sequentially for at least 5 min each).

Some mares show estrus during teasing and then fail to stand for mounting. Normal fertile mares pastured with stallions often are observed to go through periods of alternating solicitation and rejection of the stallion. This natural tendency for ambivalence may account for some of failure to stand for breeding in hand-breeding. Another factor in failure to stand for breeding appears related to severe restraint of the mare and limited precopulatory interaction with the stallion at the time of breeding.

### MATERNAL AND FOAL BEHAVIOR AND PROBLEMS

#### Normal Maternal-Foal Behavior

Key aspects of normal equine maternal behavior include (1) attending to the foal within seconds after delivery, including nuzzling, licking, and vocalization, (2) avoiding walking or lying on the neonate, (3) allowing and facilitating nursing of own, but not other foals, and (4) protecting

the neonate from intruders by positioning herself between the neonate and intruders, and even attacking or driving away intruders. Interactive bonding behavior occurs between the neonate and dam beginning at parturition and continuing for the first day or two until the selective bond is established. The foal plays an active role in eliciting maternal behavior and bonding. Even before standing, the foal reaches the head and neck to nudge and nose the dam. The foal vocalizes and responds to the vocalizations of the dam, even before standing. After standing the foal seeks the udder. Once on its feet and nursing the foal actively lingers near and returns to the mare if separated.

#### Abnormal Maternal-Foal Behavior

Inadequate or abnormal mothering behavior and bonding of mares and foals is a relatively rare, yet very urgent problem. The etiology of such behavior and the most efficient course of intervention or therapy for the various types of problems continue to be subjects of controversy. In general, problems are more common among first-time mothers, and some types of problems may recur with subsequent foals. The abnormal behavior usually occurs immediately after parturition but in some cases may emerge after 1 or several days of normal behavior. The important task is to determine the specific nature of the problem while maintaining the safety and strength of the foal and the potential for maintaining the bond.

At least six distinct categories of inadequate or aberrant behavior have been identified in mares. The simplest type is *ambivalence* with a lack of attention and protection or bonding to the foal. This is most commonly found with sick, weak, or medicated mares and/or foals, or in mares and foals separated or overmanipulated during the periparturient period. Normal maternal-foal interaction may commence as the strength of one or the other returns. In cases in which a decision is made to try to revive the bond, it is best to keep the animals together with minimal disturbance necessary for the supportive health care.

Excessive aggression toward humans or other animals seems to be related to *extreme protectiveness* of the foal. Although strong maternal protectiveness in free-running conditions may be celebrated, in the domestic situation it actually can lead to injury of the foal. While rushing to interpose herself between the foal and perceived threat, the mare may trample or push the foal into human-made obstacles in confined conditions. The intensity of such protectiveness typically subsides within a few days but may persist through weaning in rare cases.

Management aimed at avoiding evoking protectiveness when the foal is in a position where it might be trampled,

coupled with deliberate training of the mare to accept necessary intruders, usually are adequate solutions. Injuries to the young foal may be less likely when in a large stall or paddock than if in a small stall. Even when directly witnessed, protective behavior can be easily misinterpreted as attack of the foal. In open spaces, these mares rarely injure the foal, so moving the pair from a box stall to a large paddock may facilitate diagnosis. Overprotective mares tend to become even more so with subsequent foals. They often do best if allowed to foal under pasture conditions rather than in a confined foaling stall.

Some mares *fear the foal* as if it were an intruder. In such mares, normal bonding and protective behavior seem displaced by an urgency to escape from the foal, as they would in instances of fear of a pig or llama. Most of these can become tolerant with systematic desensitization (gradual introduction with reassurance and reward) as would be done for any feared novel object or situation.

*Avoidance of the foal* or aggression that is clearly limited to nursing typically, but not always, occurs with obvious udder edema and sensitivity to tactile stimulation. Positive bonding behavior and protectiveness may remain normal. For nursing avoidance or mild aggression, nursing supervision with physical restraint of the mare under halter and/or in a nursing chute in general seems to work better than tranquilization. Phenothiazine-based tranquilizers, reserpine (up to 4 mg), and benzodiazepine derivatives are possible treatments, but precautions must be taken to avoid adverse effects on the nursing foal.

*Savage attack*, a fifth type of maternal behavior problem is relatively rare but usually life threatening to the foal. The most common scenario is a sudden offensive attack, with lowered head and opened mouth biting or grasping the withers, neck, or back of the foal. The dam may lift, shake, and toss the foal against an object or stamp and hold it to the ground. In contrast to foals injured by overprotective mares, fearful mares, or mares resisting nursing, savagely attacked foals usually have bite wounds and serious multiple skeletal injuries. The only recommended practical long-term solution is permanent separation of the mare and foal. Savage attack often follows one or more days of apparently normal acceptance, bonding behavior, protection, and nursing of the foal, and it usually repeats if the mare and foal are not separated. It is for this reason that supervision, restraint, and tranquilization are rarely practical solutions to savage attack.

Savage attack of foals usually repeats with subsequent foals. A nurse mare when available is the recommended best alternate rearing situation for foals. The window of opportunity for fostering varies among mares, but usually best results are obtained with both mare acceptance and foal bonding to the mare within 3 days of parturition. The hide, blanket, fetal membranes, or feces from the biologic foal can be used to mask the "foreign odor" of the foster foal.

In busy breeding areas, breeder networks connect orphans and rejected foals with potential nurse mares (mares that have lost a foal). Also some farms that specialize in preparing "professional" nurse mares for lease to farms with orphan foals. Hand-feeding in isolation from other foals or horses is not a generally successful strategy because behavioral maladjustments in the form of inadequate socialization with horses and overattachment to humans usually ensue. Tub-fed kindergartens of several foals housed together with minimal human contact generally

have good physical and social development outcomes.

*Adoption or stealing* of the foals from other mares usually occurs during the thief mare's periparturient period. Upon foaling of her own neonate, the thief mare may abandon the stolen foal, which may not be reaccepted by its original dam. This is probably the most rare type of maternal behavior problem in horses, most commonly seen under unusual management conditions, such as induction of parturition in a large number of closely confined mares.

## STALLIONLIKE BEHAVIOR

Heterotypical behavior, that is, abnormal behavior typical of the opposite sex, in mares includes fighting with stallions; elimination-marking behavior (olfactory investigation, flehmen, and marking of excrement); herding teasing; and mounting mares. It is caused by exposure to androgens or high levels of estrogens that convert to androgen. The most common source of androgens in mares are granulosa cell tumors and administered steroids. Removal of the source of androgens generally leads to cessation of stallionlike behavior within weeks to months.

Stallionlike behavior occasionally is observed during mid pregnancy. At one time this was attributed to androgens in a male fetus, but it has been observed since in mares carrying females.

## ESTRUS CYCLE-RELATED PERFORMANCE PROBLEMS

Temperament and performance of mares can vary with the ovarian cycle, with some mares showing more or less desirable behavior during diestrus, estrus, or anestrus. Complaints require careful, detailed analysis of the specific desirable and undesirable behavior in relation to ovarian activity. Careful evaluation of complaints may reveal a physical, handling, or training problem that may be either unrelated to the ovarian cycle or that may worsen with estrus as many physical problems do. In evaluating complaints, a common finding is that owners and trainers are unaware of the specific behavioral elements of estrus and diestrus, often confusing the two states, and sometimes assuming estrus equals bad behavior. When it is confirmed that problem behaviors are associated with the ovarian cycle, improvement can be achieved with suppression or manipulation of the cycle using progesterone, hCG, and prostaglandin as recommended in Chapter 5.7: "Induction of Ovulation." A large percentage of such complaints involve submissive cowering, leaning away, and urine squirting that are easily misinterpreted as estrus. This pattern of behavior often is called "starting gate estrus" because it is common in young anxious race fillies in the starting gate.

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## CHAPTER 5.16

# Liquid Preservation of Equine Semen

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Several breed organizations within the United States now permit the use of liquid transported semen. Interest among mare and stallion owners in this technology is increasing because of advantages gained by breeding with transported semen. Unfortunately, not all stallions produce spermatozoa that survive the cooling process. Evaluation of the ability of each stallion's spermatozoa to survive the process is a quality control measure that helps ensure spermatozoal motility will be acceptable when mares are bred with cooled semen.

Stallions, the cooled transported semen of which is to be used for breeding, should be tested before the breeding season to ensure the spermatozoa survive the cooling process. If spermatozoal quality is acceptable after 24 hours of cooling, the stallion's semen probably will survive the cooling process and a recommendation can be made to use the stallion's cooled transported semen for insemination of mares. Equally important, this generates an estimate of the total number of spermatozoa that should be processed to provide an insemination dose after cooling that should maximize pregnancy rates when mares are bred.

### HEALTH REGULATIONS

Regulations regarding interstate shipment of semen are not well defined, so packaged semen often has been transported throughout the United States via passenger or express-mail air carriers without accompanying health certificates. Interstate regulations must be met to avoid unlawful shipment of semen. Some states have general health certificate requirements, and some states require special permits for transported semen. Therefore individuals intending to ship semen outside state borders should meet the requirements specified by the state of destination for the semen. State veterinarians should be contacted to obtain information regarding specific state regulations. Cooled semen must be inseminated within 24 to 48 hours after collection to achieve acceptable fertility, so this form of transported semen is generally not amenable to international shipment.

### FACTORS INFLUENCING SUCCESS RATES DURING BREEDING WITH TRANSPORTED COOLED SEMEN

Numerous factors influence pregnancy rates achieved when mares are bred with cooled stallion semen. Some of these include the number of spermatozoa inseminated, fre-

quency of insemination, concentration of spermatozoa in extender, type of extender utilized (including choice of antibiotics), cooling rate of extended spermatozoa, storage time and storage temperature before breeding, stallion variability with regard to response of spermatozoa to cooling, and inherent fertility of the stallion and mare. If quality of fresh stallion semen is poor or fertility achieved by breeding with fresh semen is poor, successful results are unlikely by breeding with cooled transported semen. Maximal success is achieved with preserved semen when screenings are performed against ejaculates of poor quality.

Other factors that affect fertility using this technology include semen collection technique, semen collection-extension interval, semen packaging technique, insemination-ovulation interval, and insemination technique. Spermatozoa are sensitive to many environmental factors, including temperature, light, physical trauma, and a variety of chemicals. Therefore any factor that negatively affects spermatozoal ability to resist environmentally induced damage adversely affects fertility achieved when using cooled transported semen for breeding.

Not all stallions produce spermatozoa that survive the cooling process. Sometimes stallion owners/managers advertise "shipped semen available" and accept contracts for breeding with transported semen when the stallion's spermatozoa do not survive the cooling process well. Improper preparation of cooled semen sometimes results in the arrival of poor quality semen that must still be used for breeding because another shipment cannot be procured before the mare needs to be bred. In such instances, pregnancy rates are suboptimal, resulting in significantly increased breeding costs and disgruntled mare owners. Stallions should be screened to see whether spermatozoa will survive cooling before their cooled transported semen is advertised for insemination of mares.

### GENERAL CONSIDERATIONS FOR TESTING ABILITY OF SPERMATOZOA TO SURVIVE COOLED STORAGE

Preservation of semen begins with the collection process. Accurate assessment of semen quality relies heavily on proper semen collection techniques. Ejaculated semen is susceptible to environmental influences. Therefore mishandling semen samples before evaluation can lead to erroneous interpretation of results, thereby negating their value for representing the ability of a stallion's spermatozoa to survive the cooling process.

Semen should be collected using a properly prepared artificial vagina. The interior of the artificial vagina should be clean and free of potentially toxic substances such as soap or tapwater residues. Between uses, artificial vaginas should be rinsed thoroughly with deionized water to remove impurities, rinsed with 70% isopropyl or ethyl alcohol to eliminate growth of microorganisms, and allowed to air dry. Before collection, artificial vaginas should be lubricated with a nonspermicidal product. Additionally, the semen collection receptacle should be nonspermicidal and fitted with a filter to allow separation of gel from the gel-free portion of the ejaculate.

After collection, semen should be processed in a careful and efficient manner. The semen should be placed immediately in a light-shielded incubator adjusted to 37° C to 38° C. All items that come in contact with raw semen should be prewarmed to 37° C to 38° C to prevent cold shock to the spermatozoa. The filtered gel-free semen should be poured into a graduated cylinder to measure volume accurately. Some types of specimen cups have inaccurate graduated markings for volume.

Sperm concentration of the gel-free semen is determined using either a hemacytometer or properly calibrated photometric instrument. The total spermatozoal number in the ejaculate is calculated by multiplying spermatozoal concentration by volume of gel-free semen. This calculation is necessary (when the percentage of progressively motile spermatozoa is taken into account) to aid in determination of the number of inseminations possible from an ejaculate and determination of the amount of semen extender that should be added to the raw semen to maximize longevity of motility following cooled storage. A portion of the gel-free semen should be diluted in a suitable prewarmed extender, then incubated at 37° C to 38° C for 5 to 10 minutes before estimation of percentage of progressively motile spermatozoa in the sample.

Motility assessment using raw (unextended) semen can yield erroneous measurements. Warmed nonfat dry skim milk-glucose (NFDSM-G) extender serves this purpose well because it sustains spermatozoal motility and does not interfere with microscopic visualization of the spermatozoa. To standardize the spermatozoal motility testing protocol, all semen samples should be diluted to a specific concentration (i.e.,  $25 \times 10^6$  spermatozoa/ml) with extender before analysis. Ideally, spermatozoal motility should be estimated at a magnification of 200 to 400 times, using a microscope equipped with phase-contrast optics and a warming stage.

Screening against ejaculates of poor quality is necessary to maximize success with preserved semen. If fresh stallion semen is poor quality, successful results most likely cannot be obtained by breeding with preserved semen. Extended semen from fertile stallions often can be stored in a cooled state for hours to days before insemination without a significant reduction in pregnancy rate. Longevity of spermatozoal viability *in vitro* may be maximized by properly diluting semen with a high quality extender, cooling the extended semen at the proper rate, and holding the cooled semen at the proper temperature until it is used.

Semen extenders contain protective ingredients that permit spermatozoal survival outside the reproductive tract. Lipoproteins, such as those contained in milk, pro-

tect spermatozoa against cold shock by stabilizing cellular membranes. Metabolizable substrates, such as glucose, provide a plentiful source of energy for spermatozoa. Antibiotics are added to extenders to retard or eliminate growth of bacterial organisms.

Osmotic pressure and pH of extenders also are adjusted to maximize spermatozoal survival. Extenders may be homemade formulations or commercially available preparations. Potassium penicillin G (1000 units per ml of extender), amikacin sulfate (100-1000 µg/ml of extender), amikacin sulfate plus potassium penicillin G in combination, or ticarcillin (100-1000 µg/ml of extender) have been found to be acceptable antibiotics for inclusion in NFDSM-G extender formulation. These antibiotics do not impair motility of stored spermatozoa and inhibit the growth of most bacteria present in equine semen. The combination of potassium penicillin G and amikacin provides better control of bacterial growth than ticarcillin or either antibiotic used singularly.

Ideally, semen should be mixed with a prewarmed (37° C to 38° C) extender within minutes after ejaculation. A minimum of a 1:1 ratio of semen to extender is recommended if semen is to be inseminated immediately. If semen is to be stored for a period longer than 2 to 4 hours before insemination, greater dilution (i.e., more extender to semen) is required. A final concentration of 25 to 50 million spermatozoa per ml in extended semen generally maximizes spermatozoal survivability *in vitro*. Alternatively, extender can be added to semen at a 1:4 to 1:19 (semen:extender) ratio to reduce seminal plasma in the ejaculate to 5% to 20% of the extended volume. Seminal plasma can be detrimental to longevity of spermatozoal viability during storage of the semen if it occupies more than 20% of the total volume of extended semen; however, retention of some seminal plasma generally improves longevity of spermatozoal motility. The concentration of spermatozoa in extended semen should not be below 25 million spermatozoa per ml. When a stallion ejaculates relatively dilute semen (e.g.,  $\leq 100$  million spermatozoa per ml), dilution in extender to arrive at a final concentration of 25 million spermatozoa per ml may fail to provide protection against environmental influences for spermatozoa, thereby resulting in a low rate of spermatozoal survival following cooled storage. In such instances, it may be beneficial to mix the raw semen with extender, then centrifuge the extended semen at  $500 \times g$  for 10 minutes, aspirate the supernatant, and resuspend the spermatozoal pellet in additional fresh extender. The majority of seminal plasma is removed after centrifugation and aspiration of the supernatant, so the remaining spermatozoal pellet can be resuspended in extender to arrive at a final concentration of 25 to 100 million spermatozoa per ml. For some stallions, centrifugation of extended semen, followed by resuspension in fresh extender, has been shown to improve spermatozoal motility characteristics after 24 hours of cooled storage at 5° C.

## COMMERCIAL SYSTEMS FOR SEMEN STORAGE AND TRANSPORTATION

Both cooling rate and storage temperature have an effect on spermatozoal survival after storage. A storage temperature of 4° C to 8° C is considered preferable as long as a

relatively slow cooling rate is permitted, especially at temperatures below 20° C. Recent studies have shown that the range of the cooling phase at which spermatozoa are most sensitive to rapid cooling is between 20° C and 5° C. Spermatozoa can be rapidly cooled from 37° C to 20° C but require slow linear cooling rate from 20° C to 5° C to maximize spermatozoal motility.

Several containers currently are available commercially that are specifically designed for slow cooling and transport of equine semen. Development of these products has made breeding with "mail-order" semen a relatively easy and successful venture for mare owners. The Equitainer I and Equitainer II (Hamilton Research, Inc., Hamilton, Mass.) are currently the most widely used containers for transporting cooled equine semen. Less expensive, disposable semen-transport containers are also available.

All these containers are passive-cooling transport devices that provide variable rates of cooling (i.e., cooling rates become progressively slower as the internal temperature is reduced). With these passive-cooling systems, cooling rates may vary according to environmental temperature and volume of extended semen being cooled. A comparative study of these containers under potentially adverse ambient storage conditions that might be encountered during air and ground transport revealed that sperm motility was adequately maintained in most of the commercially available equine semen transport containers when they were subjected to moderate (22° C) and to high (37° C) ambient temperatures. Low ambient temperatures (–20° C for 6 hours) reduced progressive spermatozoal motility in the majority of the disposable transport containers. Therefore the Equitainer containers appear to be the most appropriate containers to use when subjected to freezing conditions for an extended period of time.

### INSEMINATION DOSE (SPERM NUMBER)

The minimum insemination dose of cooled equine semen that results in good pregnancy rates is not known. Typically, mares in an artificial insemination (AI) program that uses fresh extended semen are inseminated with 250 to 500 million progressively motile spermatozoa. If fresh semen is handled carefully and is from a highly fertile stallion, the insemination dose sometimes can be reduced to 100 million progressively motile spermatozoa without reducing fertility. Because spermatozoal viability decreases with storage time, the minimum dose of progressively motile spermatozoa necessary to achieve satisfactory pregnancy rates is probably substantially higher when cooled equine semen is utilized.

The best method used to determine the insemination dose required to transport for breeding is to conduct semen-cooling trials for each individual stallion. The semen is diluted in an appropriate extender(s) as described previously, and the semen is cooled for 24 hours. The cooled semen sample is gently re-mixed after this cooling period, and an aliquot is warmed to 37° C. Spermatozoal motility is evaluated 10 to 15 minutes after warming, and the percentage of progressively motile sperm following storage is used to help ensure that future shipments will provide a minimum of 500 million progressively motile sperm after 24 hours of cooling. For example, if after 24 hours of cool-

ing the percentage of progressively motile spermatozoa is 50%, 1 billion total spermatozoa need to be prepared for shipment to ensure that an insemination dose of 500 million progressively motile spermatozoa is available for breeding a mare. Insemination volume does not appear to affect fertility, as long as the extended semen contains a minimum of  $25 \text{ to } 50 \times 10^6$  sperm/ml.

### DOUBLE INSEMINATIONS

Many stallion owners/managers prepare two bags (insemination doses) of extended semen for shipment: one to be used for an initial insemination upon arrival, and one to be held for insemination again the next day. For many stallions, the longer the semen is held at refrigerated temperature, the poorer spermatozoal motility becomes. For example, in one group of 19 mares bred with transported cooled semen at the Texas Veterinary Medical Center, seven were bred both before and after ovulation with semen prepackaged into two insemination doses contained in one semen shipment. Spermatozoa from six of those shipments was 40% or less progressively motile at the first breeding, and only 1% to 10% progressively motile at the second breeding 12 to 24 hours after the first.

Unless it is known that the semen of a particular stallion survives 48 hours of cooling, this author believes it is better to inseminate a mare with all of the transported semen as soon as practical after it arrives rather than to wait for breeding, or rather than inseminating twice 12 to 24 hours apart, with the semen in that shipment. If, however, semen is to be held for breeding again the next day, precautions should be taken to maintain the chilled semen at the proper temperature until the time of the second insemination. To reduce time and expenses involved in breeding a mare with transported cooled semen, a veterinarian should strive to minimize the number of shipments required for breeding.

### OTHER CONSIDERATIONS

When cooled semen is to be shipped for breeding a mare at another location, a processing form should be included with the semen so that personnel who will be receiving the semen can verify stallion identification before insemination and will be familiar with processing steps used when the semen was prepared. Copies of this form should also be kept in a logbook of the stallion owner to help maintain accurate records of results of each cooled ejaculate and of mares being bred. If sufficient semen is available, some semen prepared in the same manner as that shipped should be retained at the farm of origin so that semen quality can be assessed after a 24-hour storage period.

### CONCLUSIONS

The veterinarian should play a primary role in maintaining quality control (semen quality, insemination dose, timing of breeding, etc.) when horses are bred with transported cooled semen. Considerable effort is required to avoid adversarial relationships between stallion owners/managers, mare owners, and veterinarians involved in stallion and mare management. To be successful, all par-

ties must work together as a team to optimize the chance of pregnancy from each breeding.

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## on of Semen

## CHAPTER 5.17 Cryopreservation

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### STALLION EVALUATION

Before the semen is collected and frozen, a complete breeding-soundness examination should be conducted on the stallion. This procedure should include aerobic bacterial cultures from the penis, fossa glandis, preejaculatory urethra, and postejaculatory urethra. Semen should be evaluated for concentration, total spermatozoa numbers, total motility, and progressive motility. In addition, serum samples from the stallion should be tested for equine viral arteritis (EVA) and equine infectious anemia. If an unvaccinated stallion tests positive for EVA in a serum sample, further testing of the semen is required to ensure that the stallion is not shedding virus. In the interim, semen can be frozen and then thawed to evaluate how well that particular stallion's semen tolerates the freezing and thawing process.

### STRAWS

Although numerous packaging systems exist for frozen semen, the two most commonly used are 0.5-ml and 5-ml straws. The 0.5-ml packaging system usually requires multiple straws for an insemination dose, whereas the 5-ml system is usually one insemination dose. This author's preference is the 5-ml macrotube (Minitube of America, Inc., Verona, Wis.), and its use is described in this chapter.

Once the average ejaculate volume and sperm concentration for a particular stallion is known, the straws can be

The use of frozen-thawed equine semen has increased greatly over the past 10 to 15 years. The use of this type of semen can have tremendous advantages for both stallion and mare owners. Genetic material can be stored indefinitely and may be used even after the death of the stallion.

Success in the cryopreservation of stallion spermatozoa depends on a complex series of interactions among the extender, cryoprotectant, and cooling and warming rates to minimize the damage from cold shock, formation of ice crystals, and dehydration. Because semen from certain stallions seems to withstand freezing and thawing better, fertility rates vary among stallions, even under similar freezing and thawing procedures. The reason for this "stallion dependence" is not known.

In this author's experience the motility of frozen stallion semen after thawing (post-thaw) is not always a good indicator of its fertilizing capacity. Some post-thaw semen may have excellent spermatozoa motility yet never produce a pregnancy, whereas other semen with poor motility may achieve acceptable fertilization rates when used under similar conditions. In general, commercial frozen semen should have a progressive post-thaw motility of at least 25%.

This chapter is not intended to be a complete dissertation on cryopreservation of equine spermatozoa. It provides a practical procedure for this process that has worked well for this author.



ties must work together as a team to optimize the chance of pregnancy from each breeding.

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## on of Semen

## CHAPTER 5.17 Cryopreservation

JOHN V. STEINER  
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### STALLION EVALUATION

Before the semen is collected and frozen, a complete breeding-soundness examination should be conducted on the stallion. This procedure should include aerobic bacterial cultures from the penis, fossa glandis, preejaculatory urethra, and postejaculatory urethra. Semen should be evaluated for concentration, total spermatozoa numbers, total motility, and progressive motility. In addition, serum samples from the stallion should be tested for equine viral arteritis (EVA) and equine infectious anemia. If an unvaccinated stallion tests positive for EVA in a serum sample, further testing of the semen is required to ensure that the stallion is not shedding virus. In the interim, semen can be frozen and then thawed to evaluate how well that particular stallion's semen tolerates the freezing and thawing process.

### STRAWS

Although numerous packaging systems exist for frozen semen, the two most commonly used are 0.5-ml and 5-ml straws. The 0.5-ml packaging system usually requires multiple straws for an insemination dose, whereas the 5-ml system is usually one insemination dose. This author's preference is the 5-ml macrotube (Minitube of America, Inc., Verona, Wis.), and its use is described in this chapter.

Once the average ejaculate volume and sperm concentration for a particular stallion is known, the straws can be

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prepared before collection begins. Each 5-ml straw should be sealed at one end with a sealing ball, which can be of various colors for easier identification. The ball must be seated well into the end of the straw so that liquid nitrogen cannot enter the straw. To accomplish this task, the ball should be pushed in with the tip of a 10-ml syringe. Each straw should be labeled with the date of freezing, the stallion's breed, its name and registration number, and the name of the person or facility freezing semen. A permanent marking pen can be used, or the straws can be ordered prelabeled.

### FROZEN SEMEN EXTENDER

The author uses almost exclusively the B4 frozen semen extender developed by Dr. Pat Burns. The extender is made up in large batches and then divided into 50-ml aliquots, which are stored for future use. The B4 freezing extender is prepared when 70 grams of sucrose and 9 grams of glucose are dissolved in 800 ml of warm (45° C) sterile water in a 1200-ml beaker. The mixture is stirred on a magnetic stirrer for 10 minutes, and 24 g of a nonfat dry milk powder (Sanalac, Hunt Wesson Inc., Fullerton, Calif.) and 1 g of ticarcillin are added. The mixture is diluted to 1000 ml and stirred until everything is in solution. The pH should be 6.6 to 6.8 and osmolarity 348 to 360 mOsm. The extender is stored in 50-ml centrifuge tubes or in 8-oz cups at 20° C. It must be warmed to 33° C before use and mixed well. Unused aliquots are stored in a freezer.

### PREPARATION OF THE EJACULATE FOR CRYOPRESERVATION

A semen sample is collected by use of an artificial vagina with a filter. The ejaculate is evaluated for the concentration of spermatozoa, total spermatozoa in ejaculate, volume of ejaculate, and total/progressive motility of spermatozoa.

The ejaculate then is mixed in a 1:1 ratio with a skim milk/glucose extender (Box 5.17-1). This mixture then is centrifuged at 400 G at room temperature to concentrate the spermatozoa. Centrifugation times vary among stallions. Most stallions' ejaculates require 10 to 15 minutes of centrifugation to produce an ideal sperm pellet, which should be reasonably soft, without any foreign material in it. Some experimentation with centrifugation times for individual stallions may be necessary.

#### BOX 5.17-1

##### Formula for Kenney Semen Extender

Ingredient	Amount
Nonfat dry milk solids	2.4 g
Glucose	4.9 g
Deionized water	92 ml
Crystalline penicillin G*	150,000 IU
Crystalline streptomycin sulfate*	150,000 µg
7.5% NaHCO <sub>3</sub>	2 ml

\*Ticarcillin 100 mg may be substituted for penicillin and streptomycin.

While the ejaculate is being centrifuged, the freezing extender can be prepared for subsequent dilution of the sperm pellet. The final extended volume (FV) of spermatozoa in the freezing extender is determined as follows:

$$FV = \frac{\text{Total sperm}}{\text{Concentration of sperm desired in freezing extender}}$$

The concentration of spermatozoa in the 5-ml straw is generally calculated at 200 to 250 × 10<sup>6</sup>/ml. Thus for a semen sample containing 10 billion total spermatozoa, the equation is as follows:

$$FV = \frac{10 \times 10^9 \text{ Sperm}}{250 \times 10^6 \text{ Sperm/ml}} = 40 \text{ ml Final volume to be frozen}$$

Because each straw holds 5 ml, a total of eight straws (250 × 10<sup>6</sup> sperm/ml) can be prepared from an ejaculate yielding 10 billion sperm.

Once the final freezing volume is calculated, the volume of glycerol (cryoprotectant) and the volume of egg yolk that must be added to the B4 extender can be calculated as follows:

$$\begin{aligned} \text{Egg yolk volume} &= FV \times 0.08 \\ \text{Glycerol volume} &= FV \times 0.035 \end{aligned}$$

The egg yolk must be separated from the white of a fresh egg, mixed in a 1:1 ratio with Kenney extender, and centrifuged at 10,000 G for 15 minutes. The supernatant (clarified solution) is saved for use in the extension process.

### FREEZING PROCEDURE

The centrifuged tubes are examined, and sperm pellet volume is estimated. The volume of freezing extender is calculated as follows:

$$\text{Freezing extender volume} = FV - (\text{Egg yolk} + \text{Glycerol} + \text{Estimated pellet volume})$$

The egg yolk and glycerol are added to the calculated volume of freezing extender (B4). Without disturbing the sperm pellet, the supernatant is aspirated from the centrifuged semen and discarded.

Warmed B4 extender containing egg yolk and glycerol is added to the pellet, which is resuspended by gentle agitation. The concentration of extended (prefreeze) semen is measured using a hemacytometer, and the motility is estimated.

The required number of labeled straws is placed on a freezing rack. Once the extended semen is prepared, the semen and empty straws are placed in a refrigerator (5° C) to be cooled for at least 30 minutes. The straws then are loaded with 5 ml of prepared semen, and the open end is filled with a sealing ball. The position of the semen in the straw must be adjusted so that an air bubble is centered in each straw.

Liquid nitrogen is added to a Styrofoam container designed to accommodate the freezing rack. The liquid nitrogen must be 1 cm below the position of the straws on the

rack, a point that can be premeasured and the level marked on the Styrofoam container. The rack then is put into the Styrofoam container so that the straws are 1 cm above the level of liquid nitrogen, where they remain in the nitrogen vapor at approximately  $-165^{\circ}\text{C}$  for 15 minutes. The straws then are plunged into liquid nitrogen for a minimum of 10 minutes, after which they can be placed in a goblet and stored in a liquid nitrogen storage tank. If 0.5-ml straws are used, they are placed on a freezing rack approximately 3 to 5 cm above the liquid nitrogen and are left in the vapor for at least 5 minutes before being plunged into the liquid nitrogen.

### THAWING PROCEDURE

The 5-ml straws are thawed for 45 seconds in a tall (300-cm) cylindric container containing water at  $50^{\circ}\text{C}$ . A pasta storage container works well for this purpose. After about 30 seconds the contents of the straw become fluid, and the air bubble moves to the top. The straw is quickly inverted so that the air space is now at the bottom and slowly rises to the top again.

The thawed straw is removed and dried thoroughly. The semen is now ready for insemination, and one straw should be sufficient for an insemination dose. It can be used immediately or placed in a  $37^{\circ}\text{C}$  incubator for 5 to 10 minutes.

Thawing of 0.5-ml straws generally is done in a water bath at  $37^{\circ}\text{C}$  for 30 seconds. Depending on the postthaw motility and final straw concentration of spermatozoa, four to eight such straws generally are required for an insemination dose.

### SHIPPING

The management of mares to be inseminated with frozen semen is discussed in later sections of this book. The Society for Theriogenology has developed guidelines for the transport of equine frozen semen. Correct paperwork, especially the correct thawing procedure, must accompany the frozen semen and be provided to the recipient. This step is essential if optimal postthaw sperm viability is to be achieved because different freezing protocols require different thawing procedures. Any frozen semen must be recorded correctly by the recipient practitioner. An accurate inventory ensures that straws are readily available.

Frozen semen should be shipped in a properly prepared dry shipper so that it can be shipped via regular air or express courier modes. Unlike a liquid nitrogen tank, a semen shipment in a dry shipping container is not regarded as a hazardous material.

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## CHAPTER 5.18

# Artificial Insemination of the Mare with Shipped Semen

ELIZABETH METCALF  
*Sherwood, Oregon*

As more equine breed registries have sanctioned and even encouraged the use of artificial insemination (AI) with shipped semen, the industry has expanded to meet the needs of horse owners and breeders. Improvements continue to be made in the technology of transporting semen and in the opportunity for, and sophistication of, education for those involved in the use of shipped semen. Furthermore, means for assessing fertility of both the mare and the stallion also grow more precise and therefore offer greater predictability when selecting suitable candidates for breeding.

Artificial insemination, with both cooled and frozen semen, offers many advantages over natural service. It en-

ables mare owners to breed to any stallion regardless of distance, especially with cryopreserved semen. Eliminating transportation and board expenses of the mare allows use of stallions from far afield, which encourages genetic variability and hybrid vigor. Semen of known quality can be shipped in advance of breeding. In addition, less chance exists of spread of infectious diseases, both venereal and systemic, and injury to mare and stallion.

### SELECTION OF THE STALLION

Often veterinarians agree to breed a mare for a client before they have any knowledge of the stallion or his semen.

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ables mare owners to breed to any stallion regardless of distance, especially with cryopreserved semen. Eliminating transportation and board expenses of the mare allows use of stallions from far afield, which encourages genetic variability and hybrid vigor. Semen of known quality can be shipped in advance of breeding. In addition, less chance exists of spread of infectious diseases, both venereal and systemic, and injury to mare and stallion.

### SELECTION OF THE STALLION

Often veterinarians agree to breed a mare for a client before they have any knowledge of the stallion or his semen.

It is perhaps beneficial for a successful, or at least a more predictable, outcome if the veterinarian is involved in the selection of the stallion. The mare owner first should select several potential stallion candidates for their mare. Conversations should then take place between the mare owner's veterinarian and the breeding manager and/or veterinarian of the stallion regarding the stallion's past and present fertility with shipped semen, his availability, the dosage of sperm that will be shipped, the specific shipping schedule and means, and the specific person to contact when the mare is ready for semen. Much information regarding the fertility of the stallion and his management can be gleaned from this initial conversation.

A multitude of tests evaluate fertility of stallion semen but the most informative measure is foaling rate. Although no single *in vitro* laboratory test has proven to correlate precisely with stallion fertility, stallions whose semen demonstrates a high percentage of morphologically normal, progressively motile spermatozoa with little reduction in motility over the first 24 hours of storage often prove to have better fertility than those that lack these attributes. Other means of predicting stallion fertility with *in vitro* tests include floccytometric analysis of sperm membranes, organelles, and DNA, computer-assisted motility analysis, glass wool/Sephadex bead filtration, binding and penetration assays, and antisperm antibody assays. Unfortunately, because of expense, most stallion semen is not evaluated routinely by such sophisticated testing.

Some signals for concern regarding selection of a stallion include the following:

1. A stallion manager who boasts that the stallion has a copious volume of semen in each ejaculate (without mentioning concentration) and the company does not centrifuge it
2. Statements that the entire ejaculate will be shipped to ensure conception (a single ejaculate of a normal stallion should contain adequate sperm to cover far more than a single mare)
3. Claims that it is not necessary to calculate the concentration of the semen at every collection before extending it for shipment, or that the semen **MUST** be shipped same day air to ensure motility and/or fertility

On the other hand, many conscientious and astute stallion managers may inform the receiving veterinarian that after years of evaluating pregnancy data on a certain stallion, the breeding dose may contain less total number of motile sperm than expected. Often these managers are well aware of the minimum sperm number needed in a single breeding dose to achieve optimum pregnancy rates in a single heavily booked stallion. One should not be deterred from breeding to a stallion so carefully managed.

## PREPARATION OF THE MARE FOR ARTIFICIAL INSEMINATION

The ultimate goal of insemination is to provide semen in a time frame that coordinates the availability of capacitated spermatozoa with the arrival of the transported oocyte within the mare's oviduct. It is also the responsibility of the veterinarian to ensure the optimum in-

trauterine environment that supports the developing embryo. With these objectives in mind, preparation of the mare begins well in advance of the actual anticipated breeding date.

Too often, the fertility of the mare is somewhat overlooked and she is selected as a broodmare candidate simply due to her availability. Truly, her potential fertility needs to be as carefully evaluated as the fertility of the stallion. A breeding soundness examination (BSE) should be performed at the beginning of the breeding season that is based on her age and parity. The BSE may range from a rectal and ultrasonographic examination of the reproductive tract to a cytology, culture and/or biopsy of the endometrium to a videoendoscopic examination of the endometrium. Inclusion of an ultrasound examination at every rectal exam enhances the continual education of the veterinarian and aids in detection of many changes that are not palpable, thereby increasing pregnancy rates.

In young maiden mares, especially those that have never raced, a rectal and ultrasonographic exam may constitute a sufficiently adequate prebreeding examination. In this author's opinion, in the foaling mare a cytologic evaluation of the endometrium should be included. This test is a simple stall-side procedure that provides immediate information on the status of the lining of the endometrium. If significant numbers of polymorphonuclear leukocytes (PMNs) are present on the smear, the mare has endometritis and its etiology needs to be investigated before proceeding with insemination. Bacteria and yeast forms also may be detected with a cytologic exam.

During the estrous phase of the heat cycle, an ultrasound examination of the reproductive tract usually supports the rectal palpation findings of a dominant, growing follicle, in addition to the classic "spokewheel" pattern of endometrial edema, which may be subjectively quantified. The ultrasound examination also may demonstrate the presence of echogenic particles within the follicle in addition to increasing echogenicity of its wall—both indicative parameters of ovulation within the next 24 hours. Although the duration of heat in the mare may be variable, most mares ovulate near the end of this estrous phase. Interestingly, the edema is less apparent on ultrasound just before ovulation. Because the timing of insemination with respect to ovulation is so critical, the presence or absence of this edema can be a powerful tool used to optimize pregnancy rates through the control of ovulation timing. A more detailed discussion is provided in Chapters 5.7 and 5.14.

A number of agents that shorten the interval to ovulation in the mare have been investigated. The most effective agents possess luteinizing hormone (LH) activity with varying degrees of follicle stimulating hormone (FSH) activity. Human chorionic gonadotropin (hCG) with its potent LH-like activity, is, at the time, the least expensive and perhaps the most popular agent used for the induction of ovulation. It has been reported to be effective at doses ranging from 1000 to 5000 IU given intramuscularly, intravenously, or subcutaneously. The author tends to base the dosage on size of the mare; very large breeds receive larger doses and breeds such as the Miniature Horse or small ponies receive the minimum dose of hCG.

The use of hCG in the mare is somewhat controversial. First, with its repeated use, antibody development has been documented in several studies; however, the clinical impression of many practitioners is not in agreement with these studies. Secondly, mare owners often complain that their mares experience pain associated with administration of some hCG products. Finally, the reliability of hCG in its ability to hasten the interval to ovulation, especially in the older or compromised mare, has been questioned. Regardless of its potential disadvantages, hCG remains a popular, inexpensive and effective means of inducing ovulation in the majority of mares.

Synthetic gonadotropin-releasing hormone (GnRH) analogs (deslorelin acetate and buserelin) also have proved effective in inducing ovulation. Although the use of these latter agents may delay slightly the mare's return to estrus if she fails to conceive, in this author's experience these GnRH analogs are more reliable in inducing ovulation, especially in mares more prone to ovulation failure. These include older mares, mares in vernal transition, and mares concomitantly treated with prostaglandin inhibiting agents such as many of the antiinflammatory drugs.

Ovulation-inducing agents are far more reliable and effective if given at the appropriate time during estrus. If endometrial folds are apparent on the ultrasound examination, and a dominant softening follicle is present (usually >30 mm in diameter) hCG, deslorelin acetate, and busere-lin are expected to hasten ovulation on average of 36, 41 to 48, and 24 to 48 hours, respectively, after administration of the induction agent. Samper (see readings list) reported that 98% of mares with maximal endometrial edema given hCG or deslorelin would consistently ovulate with 48 hours of administration.

## ARTIFICIAL INSEMINATION

In natural mating, the stallion's penis penetrates the relaxed cervix of the mare and upon ejaculation, deposits semen in her uterus. The ejaculate contains forceful "jets" or pulses of semen that may immediately reach the distal uterine horns or oviductal papillae. The rhythmic thrusts of the stallion's penis may serve to massage the mare's vagina, thereby stimulating uterine contractions that further propel sperm towards the oviducts. The characteristically engorged stallion penis may prevent the outflow of semen from the vagina immediately after ejaculation.

In an attempt to mimic the events of natural mating and yet ensure minimal contamination of the mare's reproductive tract, the following protocol is recommended. The mare should be properly restrained, preferably in stocks to protect the inseminator. Other devices, such as a twitch, have been used effectively for restraint but are usually unnecessary. If chemical restraint is warranted, the use of  $\alpha_2$ -agonists such as xylazine, may be preferable to other agents because of their effect on contractility of the mare's uterus while it is under the influence of estrogen, particularly in mares that exhibit a delay in uterine clearance after insemination.

The mare's tail is bandaged and tied away from contact with the vulva and perineum. The vulva is washed well with liquid soap and rinsed thoroughly with water. This procedure is repeated a minimum of three times, until the area is visually free of any debris. The vulva and perineal

area then should be dried with a clean paper towel.

The inseminator dons a sterile sleeve and grasps a sterile insemination pipette between thumb and palm to ensure that the tip is protected in a sterile environment (Figure 5.18-1). If breeding with 0.5-ml straws of frozen-thawed semen, an insemination gun may be used instead of the pipette. Nonspermicidal sterile lubricant is applied sparingly to the sleeve covering the forefinger. Prepared semen should be contained in a nonspermicidal syringe and protected in the nonsterile hand from adverse environmental conditions such as UV light, cold, heat, and air.

The inseminator inserts the sleeved hand, continuing to protect the tip of the insemination pipette, through the lips of the mare's vulva (Figure 5.18-2), into the vaginal vault, and inserts one to two fingers through the cervical os. The finger(s) then act as a guide for advancement of the insemination pipette through the cervix and approximately 1 cm into the mare's uterus. If the pipette has



**Figure 5.18-1** The tip of the sterile artificial insemination pipette is carefully guarded with the thumb against the palm of the inseminator.



**Figure 5.18-2** The pipette continues to be guarded in the palm of the inseminator as it passes into the vagina of the mare.

not encountered resistance once in the uterus, it can be carefully and gently advanced into the desired (usually ipsilateral to the developing follicle) uterine horn. This is not always possible due to the amount of endometrial edema and folding, so extreme care must be taken to avoid damaging the endometrium. Once the pipette is satisfactorily in place, the plunger of the syringe is depressed and semen is deposited in the uterus. If resistance is encountered when the plunger is depressed, the tip of the pipette may be against the endometrium and requires repositioning. A small amount of air may be introduced to clear the pipette. Massage of the vaginal vault during withdrawal of the inseminator's hand may stimulate uterine contraction and aid in propulsion of spermatozoa to the uterotubal junction (UTJ).

### OPTIMIZING PREGNANCY RATES WITH ARTIFICIAL INSEMINATION

Pregnancy rates with transported cooled semen have been reported to range from less than 20% to greater than 80%. Although somewhat dependent on the fertility of the

mare and stallion, the extreme variability often is due to other management factors. These factors include handling and management of the stallion, handling and management of the semen, extension of the semen, shipment of the semen, number of motile sperm inseminated, management of the mare, preparation of the mare for breeding, insemination technique, handling of the semen during insemination, and postinsemination management of the mare. Therefore pregnancy rates reflect the fertility of the horses and the expertise and conscientiousness of the humans involved in this endeavor.

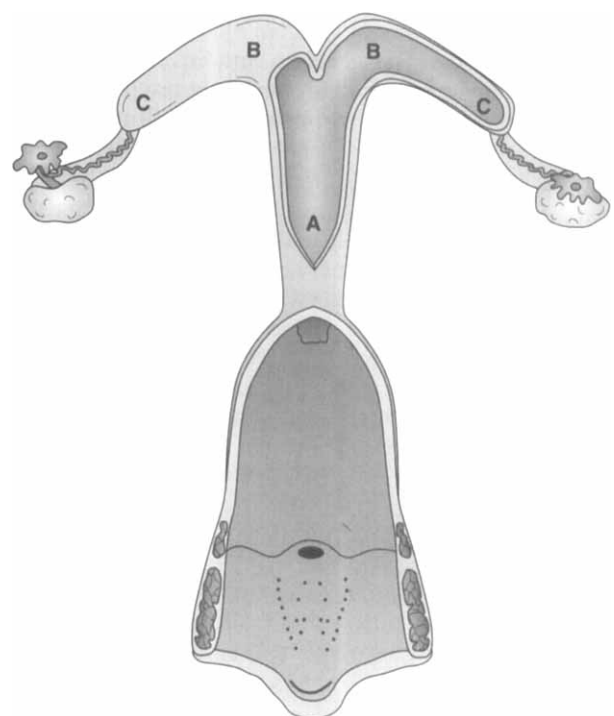
Pregnancy rates with frozen-thawed semen also demonstrate a wide range of success. Cryopreserved semen has lower fertility than cooled semen but this could be due, at least in part, to the intensive management often required for success with frozen semen. Although many investigators have demonstrated acceptable per cycle pregnancy rates of 25% to 45% when either breeding every 24 hours or postovulation, much higher pregnancy rates (>70% per cycle) have been achieved with very intensive mare management and pre- and postovulation breeding. Furthermore, the results of a recent study performed by Loomis (see readings list) demonstrate no significant difference in first cycle pregnancy rates, seasonal pregnancy rates or number of cycles per pregnancy between cooled and frozen semen shipped from his facility to a large number of mare owners (Table 5.18-1). In this study, the inseminators were instructed to breed the mares with the frozen thawed semen both pre- and postovulation and close to ovulation. Here, management and selection of the stallions was optimal, and the stud farm personnel were thoroughly instructed and closely involved with election and insemination of the mares as well.

The site of semen deposition has received great attention recently. Although pregnancy rates appear to be in-

Table 5.18-1

Pregnancy Rates from Cooled and Frozen Semen

Parameter	Cooled	Frozen
Number of stallions	16	106
Number of mares	850	876
First-cycle pregnancy rate	59.4%	51.3%
Seasonal pregnancy rate	74.7%	75.6%
Cycles/pregnancy	2.06	2.08



**Figure 5.18-3** A diagram of the uterus: sites of semen deposition for AI. A, Uterine body; B, uterine horn; C, uterotubal junction at oviductal papilla. (Courtesy Molly McAllister, Portland, Ore.)

dependent of volume of semen, extremely small volumes and numbers of motile spermatozoa (as low as  $1 \times 10^6$  motile sperm) deposited either at the uterotubal junction or within the oviduct have shown promising pregnancy results. Furthermore, deep uterine insemination also enhances pregnancy rates. This procedure, as described by Rigby and colleagues, entails passage of the insemination pipette through the cervix into the uterine body. It is then directed into the uterine horn ipsilateral to the dominant follicle. Through transrectal manipulation, the pipette is moved into the horn by gently threading the uterus around the pipette, as would be done in the cow. However, because of the degree of edema of the mare endometrium during estrus, extreme care must be taken to avoid damaging the endometrium with this technique. The placement of the insemination dose for these procedures is depicted in Figure 5.18-3.

### DOSAGE OF COOLED SEMEN FOR ARTIFICIAL INSEMINATION

The minimum insemination dose required for maximal pregnancy rates has long been accepted to be  $500 \times 10^6$  progressively motile spermatozoa inseminated every 48 hours into mares in estrus until ovulation occurs. Jasko and colleagues (see readings list) have further reported that the semen must be extended to 25 to  $50 \times 10^6$  motile sperm per ml to achieve maximal pregnancy rates. As mentioned previously, this minimum dose, and not the final concentration, may actually be stallion-dependent.

Often more than a single dosage of semen is shipped. The question arises whether the unused doses should be maintained at  $4^\circ\text{C}$  or immediately inseminated into the mare. Supporters of the "equitainer" hypothesis argue that the sperm storage sites in the mares oviduct are filled with the first insemination and will not need to be replenished for at least 24 hours. Therefore using the mare as the incubator for the second dose is wasteful because the excess spermatozoa will be expelled. Those in favor of the mare as the optimal reservoir believe that although the motility of the second dose of semen fares well in the equitainer, it does not necessarily reflect the fertility of this dose and therefore will fare better in the mare.

The studies that have addressed this argument have either used few stallions in the experimental design, or failed to take into account the interval from insemination to ovulation. However, Heiskanen and colleagues (see readings list) have shown that mares bred with semen stored at  $5^\circ\text{C}$  for up to 40 and 80 hours have acceptable pregnancy rates of 87% and 65%, respectively, thus demonstrating acceptable pregnancy rates with stored semen. Still, the optimal means for preserving the fertility of "extra" doses of semen remains a controversial subject and the answer is not entirely clear, perhaps because again, the fertility may vary with individual stallions and mares.

If a suboptimal dose of semen is shipped, the semen may be improperly extended, the sperm numbers may be low, or the motility or morphology may be poor. If the total volume of semen is not so great that it is expelled

through the cervix upon insemination, every attempt should be made to inseminate enough semen to make up the optimal dose for pregnancy. If the volume is too great, centrifugation may be tried but the author has found poor results with motility of shipped semen that has been centrifuged. Therefore it is perhaps best to reinseminate the mare 6 to 12 hours after the first insemination with a second dose in an attempt to "cover" her with an optimal dose over 24 hours.

### DOSAGE OF FROZEN SEMEN FOR ARTIFICIAL INSEMINATION

The number of morphologically normal, progressively motile sperm that yields optimal pregnancy rates with frozen-thawed semen is likely, again, to be stallion and management dependent. Most investigators suggest that a minimum of  $200 \times 10^6$  progressively motile sperm are necessary for an optimal breeding dose; many require and inseminate with a higher number. This author prefers to inseminate at least  $300 \times 10^6$  motile sperm both pre- and postovulation, with only a 6- to 8-hour interval between inseminations (with ovulation occurring during this interval). Although the physiologic endometritis that ensues in response to the sperm in the first insemination is greatest at 6 to 12 hours after insemination, pregnancy rates do not appear to be adversely affected with this protocol.

### TIMING OF INSEMINATION

With the use of cooled semen, mares should be inseminated within 24 hours before ovulation, which allows ample time for capacitation of the spermatozoa and transport to the oviduct. Excellent pregnancy rates have been achieved when mares are inseminated even greater than 48 hours before ovulation, suggesting that sperm can survive in the oviduct for long periods of time. If mares are bred with cooled semen after ovulation, pregnancy rates and embryo quality decrease significantly.

When frozen-thawed semen is being used, insemination should be as close to ovulation as possible because it is suspected that the thawed spermatozoa are unable to survive as well in the mares' reproductive tract. Many veterinarians and technicians prefer the ease of breeding after ovulation because it is difficult to predict ovulation and valuable semen can be wasted if the mare fails to ovulate in a reasonable time period following insemination. However, per cycle pregnancy rates after postovulation breeding usually are not as high as pregnancy rates when mares are inseminated both before and after. Some stallions are exceptions to this general rule however. Some of the highest per cycle pregnancy rates ( $>70\%$ ) reported occur in mares bred under the sample protocol suggested in Table 5.18-2.

In conclusion, it remains clear to many who work in this industry that numerous factors are beyond their control in this role of "facilitators" of nature. Still, careful and conscientious management of breeding stock allows many to enjoy the vast benefits of AI with both fresh and frozen semen.



Table 5.18-2  
Sample Protocol for Insemination with Frozen Semen

Day	Stage	Procedure
1-4	Early estrus	<ul style="list-style-type: none"> <li>Examine mare daily via rectal palpation and ultrasound.</li> <li>Perform cytologic evaluation/culture for bacteria, if necessary.</li> </ul>
5	Edema present	Examine mare daily in morning.
6	Dominant follicle developing Maximal edema	Administer hCG or GnRH analogue (deslorin).
7	Dominant follicle softening at 10 AM (a) Edema decreased Follicular wall thickened (b) Edema absent Soft, irregular follicle (c) No edema	Examine at 10 AM.  Examine at 4 PM.  Perform first insemination at 10 PM.
8	Follicle "ripples" with pressure (a) Corpus hemorrhagicum No intraluminal fluid in uterus (b) Corpus hemorrhagicum No intraluminal fluid in uterus	Perform second insemination at 6 AM.  Reevaluate for fluid in the afternoon; treatment if necessary.

*hCG*, Human chorionic gonadotropin. *GnRH*, gonadotropin-releasing hormone.

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## CHAPTER 5.19

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# Management of the Embryo Donor and Recipient Mare

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Numerous reports have described the factors affecting pregnancy rates after embryo transfer. Undoubtedly, the most important factor affecting pregnancy rates is management of the donor and recipient mare. Information in this chapter focuses on selection of the donor and recipient and aspects of mare management shown to affect the success of an embryo transfer program.

Equine embryo transfers have been performed routinely for the past two decades. One of the primary uses of embryo transfer is for older mares that fail to provide live foals by traditional breeding practices. The second most common use of embryo transfer is to increase production from genetically superior mares thus allowing a greater genetic influence of the dam. Although some breeds oppose the multiple registration of foals in a given year, other breeds have no restrictions. Embryo transfer also has the advantage of allowing the mare to remain in competition (racing, cutting, showing) while still providing a foal. The use of embryo transfer has increased in the United States modestly over the past two decades. Other countries that have a considerable embryo transfer industry include Argentina, Brazil, and Australia.

### SELECTION AND MANAGEMENT OF DONOR MARES

Several factors must be considered in selecting a mare as a donor for an equine embryo transfer program, including cost of the procedure, reproductive history of the mare, the stallion or semen to be used, breed registry guidelines, potential value of the foal, and the number of pregnancies desired. A thorough knowledge of the mare's reproductive history should allow embryo transfer personnel to give an estimate of the amount of time needed to obtain a pregnancy from the donor mare. Mares less than 16 years of age with good reproductive histories when bred to fertile stallions generally provide an embryo approximately 60% of the time. In contrast, mares with histories of infertility have a very poor prognosis of embryo recovery (<30%). Many times acute or chronic endometritis prevents the donor from becoming or remaining pregnant. In addition, viability of the oocyte from the aged mare (greater than 18 years) is reduced greatly. The selection of the stallion or semen to be used in the embryo transfer program is extremely important. The use of fresh semen from a stallion is ideal, although, in most cases transported cooled semen, if used within 24 hours of collec-

tion, does not result in a depression of fertility. In most cases the use of frozen semen in an embryo transfer program is counterproductive. Very few stallions have the same fertility with frozen semen as with fresh semen. Therefore embryo recovery is reduced when mares are inseminated with frozen semen.

The mare owner should have a current knowledge of the breed registry guidelines. This prevents costly mistakes by the breeders. On several occasions embryo transfer foals have been produced and have been denied registration by the breeds because of failure to obtain embryo transfer permits or proper blood typing or DNA identification. Mare owners should contact their breed registry before enrolling a mare in an embryo transfer program to obtain the latest regulations on requirements for foal registration.

Preferably each donor mare undergoes a complete reproductive evaluation before collection of embryos. Breeding soundness exam should include examination of the external genitalia. On some occasions it is best to perform reproductive surgery on the mare before enrolling her in an embryo transfer program. Particular attention is given to the size and tone of the uterus, and the size, shape, and tone of the cervix. The genital tract also is examined by ultrasonography to detect any signs of pathology such as uterine fluid, cyst, or air. The cervix is examined vaginally for evidence of adhesions, tears, or other abnormalities. Uterine swabs for culture and cytology also are obtained. A uterine biopsy is obtained from the body or horn of the uterus. If examination provides evidence of uterine infection, treatment is initiated immediately. Generally the initial ultrasound examination is performed on day 2 or 3 of estrus to monitor follicular and uterine changes. Examinations are continued daily until ovulation. If at all possible, the donor mare is teased with a stallion daily or every other day during the breeding season. Mares in estrus should have evidence of estrogen production based on the presence of endometrial folds. The folds are scored from 0 to 3; 0 equal no folds, 3 equals extreme edema.

In most cases the stallion is not on the same premise as the donor mare. Breeding the mare with fresh semen from a resident stallion apparently maximizes embryo recovery. Under those conditions, timing of insemination may not be as critical because fresh semen is likely to be available upon request. In contrast, insemination of donor mares with cooled, shipped semen or frozen semen requires close synchrony between insemination and ovulation. Based on ultrasonography, once the donor mare has acquired a

35- to 45-mm follicle she is ready to be administered an ovulatory agent, either hCG (Chorulon) or deslorelin (Ovuplant). Selection of the ovulatory agent depends on the age of the mare and the number of times that the mare has been given hCG previously. Numerous reports have indicated that older mares more often fail to respond to hCG and mares that have been given two or three injections of hCG in a breeding season also may fail to respond. Therefore deslorelin often is used in these categories of mares. However, if it is the first cycle of the year and if the donor mare is a young or middle-age mare then hCG is selected as the hormone of choice. Generally, if the semen can be obtained within 24 hours then the mare is given the ovulatory agent and inseminated the following day.

Many of the donor mares in an embryo transfer program are mares that are susceptible to postbreeding endometritis. The donor mare must be examined within 12 to 24 hours after insemination. If a large amount of uterine fluid is present, then the donor mare's uterus must be lavaged with sterile saline or lactated Ringer's solution to remove the debris. However, if only a small amount of clear fluid is present in the mare's uterus, then administration of oxytocin may suffice in elimination of the uterine fluid. In some of the more problematic cases the uterus should be examined 4 to 6 hours after insemination and flushed to remove uterine fluid. Treating the mare's uterus with antibiotics for 3 days postbreeding also may be necessary to prevent reinfection.

With frozen semen, if two or more doses of semen are made available each cycle, then the following strategy would be used in breeding the donor mare. Once a mare has obtained a 35- to 45-mm follicle she would be administered human chorionic gonadotropin (hCG) or gonadotropin-releasing hormone (GnRH) according to criteria described previously. At 24 hours and 40 hours after hCG or GnRH administration the mare is inseminated with a dose of semen. If only one dose of frozen semen is provided per cycle then the mare would be examined daily with ultrasonography up until 24 hours after hCG administration. At that time she would be placed on a four times per day examination (q6h) and inseminated with the one dose immediately after ovulation has been detected. Mares are assigned for embryo recovery either 7 or 8 days after ovulation. Over the past several years all of the embryo recoveries in this author's laboratory have been performed 8 days after ovulation. Particularly with older mares embryonic development may be retarded and thus embryo recovery is higher for day 8 versus day 7 flushes.

## SELECTION AND MANAGEMENT OF RECIPIENTS

Selection and management of recipient mares for an embryo transfer program is the most important factor affecting pregnancy rates. On farms handling only one or two donors, recipient mares may be purchased from local backyard horse owners who are familiar with the mare's reproductive history. However, acquiring a large number of recipient mares requires that mares be purchased from local sale barns. Thus the reproductive history of these mares is unknown. In either case the recipient mare

should meet the following criteria: 900 to 1200 pounds; 3 to 10 years of age; and broken to halter. The effect of size of recipient on the subsequent size of the foal has not truly been determined. However, the size of the donor mare should be matched with the recipient as nearly as possible. This may be difficult when obtaining embryos from large warmbloods or draft horses.

Typically nonlactating mares are easier to use in an embryo transfer program than a mare that is lactating. If a lactating mare is not being used, the animals should not be used as recipients until at least the second postpartum cycle. Numerous types of recipient mares can be used: ovarian-intact cycling mares; ovariectomized mares; mares in anestrus; and mares during the transitional period. This author prefers to use ovarian intact normal cycling mares. However, pregnancy rates using ovariectomized, progesterone-treated mares have been shown to be similar to ovarian-intact mares.

Occasionally, early in the year a scarcity of normal cycling mares occurs. The alternative at that time of the year is to use either an anestrous mare or a transitional mare. In this author's experience transitional mares are more appropriate to use than truly anestrous mares. Mares in transition should be selected based on the presence of endometrial folds. This indicates that estrogen is being secreted. Transitional mares can then be placed on progesterone at the time of the donor mares ovulation. The suggested progestin treatment for either ovariectomized mares or transitional mares includes altrenogest (Regumate) daily or 150 mg of progesterone injected daily. With the use of ovariectomized mares, progesterone treatment must continue until the placenta begins to produce progesterone at approximately 100 to 120 days. With transitional mares, progesterone treatment may be terminated once the mare has ovulated and developed secondary corpora lutea during early gestation.

The recipient mare should be examined by rectal palpation and ultrasonography before purchase. The external genitalia are observed for normal conformation. Those mares with poor external conformation that may predispose them to wind sucking are generally rejected. Mares are then palpated per rectum and the size and tone of the uterus, cervix, and ovary are determined. The uterus and ovary are then examined with ultrasonography. Evidence of pathology such as uterine fluid, uterine cyst, ovarian abnormalities, or the presence of air or debris in the uterus would render the mare unsuitable for purchase as an embryo recipient. In addition, any mare found to be pregnant is not purchased unless the pregnancy is less than 30 days.

Approximately 15% to 20% of the mares initially presented are rejected. Mares that pass the initial examination are given a breeding soundness exam similar to the exam of the donor mare. Recipients are vaccinated for influenza, tetanus, and rhinopneumonitis and are quarantined from other mares for at least a period of 30 days. Those mares that are in thin condition are fed a concentrate ration and a free-choice alfalfa hay. The majority of recipients are purchased in late fall and placed on a 16-hour lighting regimen beginning December 1. Starting approximately February 1, mares are palpated and examined with ultrasonography twice per week until a follicle greater than 35 mm is obtained. Mares with follicles greater than 30 mm are examined daily with ultra-

sonography until ovulation. Ideally, recipient mares should have one or two normal estrous cycles prior to being used as a recipient. Mares are excluded as potential recipients if they consistently have erratic or abnormal estrous cycles.

Hormonal manipulation of the recipient mare's estrous cycle is an important component of an embryo transfer program. The degree of hormonal manipulation is dependent upon the size of the embryo transfer operation. Smaller operations that deal with only one or two donors use more hormonal manipulation than larger operations that may have a large number of donors and recipients. Small operations should place the donor and one or two recipients on progesterone for 8 to 10 days and then administer prostaglandins on the last day of treatment. The progesterone can either be altrenogest used daily or injectable progesterone at a level of 150 mg daily for the same length of time. It is not uncommon to use a combination of progesterone and estrogen (150 mg progesterone, 10 mg estradiol-17 $\beta$ ) daily for 8 to 10 days followed by prostaglandins.

The donors and recipients will ovulate 7 to 10 days after prostaglandin treatment. Generally, having the recipient ovulate either 1 day before or up to 3 days after the donor mare is desirable. This can be accomplished by using hCG (Chorulon) or GnRH (Ovuplant) to induce ovulation in either the recipient or donor mare to provide optimal synchrony of ovulation. In a larger embryo transfer station it is common to manipulate the cycle by using only prostaglandins, hCG, or GnRH. Typically the ovulation dates of the recipient are recorded and once a donor mare ovulates then a recipient is selected that has ovulated either 1 day before or up to 3 days after the donor. If a mare is not used as the recipient she is then given prostaglandins 9 or 10 days after her ovulation and induced to return to estrus.

Each recipient mare is given a final examination 5 days after ovulation before to being used as the recipient. Mares are classified as acceptable, marginal, or nonacceptable based on this 5-day exam. The 5-day exam includes palpation per rectum for uterine and cervical tone, and ultrasonography of the uterus and ovaries. An acceptable recipient should have a round, tubular, firm uterus and a closed cervix. She also would have the absence of endometrial folds, a normal sized uterus, and the presence of a visible corpus luteum. Mares generally are placed in the marginal category based on a decrease in uterine tone or cervical tone or perhaps the presence of grade 1 endometrial folds. Unacceptable recipients typically have poor uterine tone, a soft-open cervix, or presence of endometrial folds and/or fluid in the uterus. A retrospective examination of this author's commercial embryo transfer program has revealed that the 5-day check is the best predictor of whether or not a recipient mare will become pregnant.

Embryos are transferred either surgically by flank incision or nonsurgically. Most of the embryo transfer stations are now using nonsurgical transfer methods. The details of the transfer methods are presented in the subsequent chapter. Mares are examined with ultrasonography for

pregnancy detection 4 or 5 days after transfer. Mares that are diagnosed pregnant are reexamined on days 16, 25, 35, and 50. Mares not confirmed pregnant on the initial examination (day 12) are reexamined 2 days later. If the ultrasound scan continues to be negative the mare is considered not pregnant and given prostaglandin to induce estrus. Unless the embryo was extremely small (<150 microns) the majority of mares that are to be pregnant have a visible vesicle at 12 days of gestation. Those mares in which the vesicle does not appear until 14 or 16 days of gestation have delayed embryonic development and are more likely to suffer early embryonic loss. The initial ultrasound examination allows the breeder to decide whether to rebreed the donor and attempt a second embryo recovery. The ultrasound exam at 25 days determines whether a fetus is present with a viable heartbeat. The majority of losses that do appear in embryo transfer recipients occur between days 12 and 35. However, early embryonic loss before 50 days of gestation appears to be no greater in embryo transfer recipients than other pregnant mares that are inseminated with either fresh or cooled semen. Mares that fail to become pregnant after an embryo transfer are generally used a second time but not a third. The pregnancy rates on mares receiving an embryo on a second attempt are no different than those that receive an embryo only one time and become pregnant.

Pregnant recipients should be fed a maintenance ration similar to other broodmares during the first two thirds of gestation and then administered extra energy in the form of concentrate rations during the final one third of pregnancy. Recipients should be monitored closely around the time of impending parturition. Management procedures identical to those used for foaling broodmares should be used. No greater difficulty in foaling embryo transfer recipients than normal broodmares has been found. The influence of the size of the recipient versus size of donor on ease of foaling has not been adequately studied, although this does not appear nearly as critical in horses as it does in cattle.

In summary, a relatively high pregnancy rate can be anticipated in an embryo transfer program if management of the donor and recipient mares are maximized. Attention should be given to selection of both donor and recipient, nutrition, proper monitoring of the donor and recipient with palpation per rectum and ultrasonography, careful assessment of the recipient, and management of the recipient after embryo transfer. Day 12 pregnancy rates for either fresh or cooled semen should be 75% to 80% and those at 50 days of gestation should be 65% to 70%.

### ***Supplemental Readings***

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## CHAPTER 5.20

# Embryo Collection, Storage, and Transfer

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Embryo transfer continues to be the most widely used assisted reproductive technique for mares. This method is routinely used to obtain (1) foals from performance mares, (2) multiple foals from individual mares each year, (3) foals from 2-year-old mares, (4) foals from reproductively unsound mares, and (5) foals from mares with nonreproductive health problems. Although embryo transfer was initially proposed as a promising method to obtain foals from aged, subfertile mares, experiments with oocyte transfer and embryo transfer have documented that many oocytes/embryos produced by aged, subfertile mares are inherently defective and have low survival rates after transfer to recipient mares. Therefore aged, subfertile mares are not optimal candidates for embryo transfer.

The first successful equine embryo transfer was reported in the early 1970s; however, it was not until the early 1980s that embryo transfer became an accepted clinical procedure in the equine breeding industry. At that time widespread use of embryo transfer was limited by the need to maintain recipient mares at the site of embryo collection or to transport donor mares to a centralized embryo transfer facility. In the late 1980s a technique for cooling equine embryos was invented that led to the development of a practical method of short-term (<24 hr) storage and transportation of equine embryos. That breakthrough allowed embryos to be collected in the "field" and then shipped to a centralized facility for transfer to suitable recipient mares. The ability to transport cooled embryos allowed veterinarians to offer embryo transfer service without the onerous task of maintaining recipient mares and eliminated the need to transport donor mares to a centralized facility. This chapter reviews current techniques for the collection, storage, and transfer of equine embryos. The procedures used for the reproductive management and synchronization of donor and recipient mares are discussed elsewhere in this volume.

### EMBRYO COLLECTION

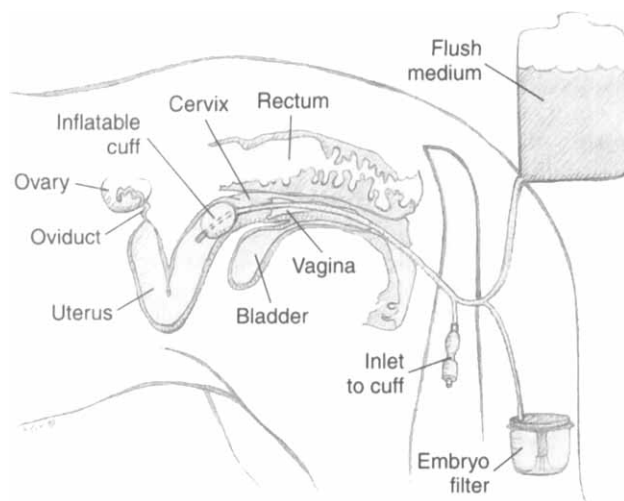
Equine embryos are selectively transported through the oviduct into the uterus between days 5 and 6 postovulation (ovulation = day 0), at which time they are at the late morula to early blastocyst stage of development. In contrast unfertilized oocytes remain trapped in the oviduct where they degenerate over a period of several months. Although embryos can be recovered on days 6 to 9 post-

ovulation, the decision of when to perform an embryo collection is influenced by several factors. Embryos that will be transferred immediately after collection or cooled for short-term storage before transfer are generally collected on day 7 or 8 postovulation, and embryos that will be frozen for long-term storage are collected on day 6 postovulation. Embryos are not routinely collected on day 9 because their transfer success rate has typically been lower than that for day 7 or 8 postovulation embryos. The lower transfer success rates reported for Day 9 embryos, however, have been based on surgical transfer procedures. More recent results obtained with nonsurgical transfer procedures have indicated that the transfer success rates for day 9 postovulation embryos can be equivalent to those of day 7 and 8 postovulation embryos.

In addition to these factors, personal preference and scheduling considerations may dictate the day an embryo collection is performed. This author's current preference is to perform embryo collection on day 8 postovulation for embryos that will be transferred immediately after collection or cooled for short-term storage before transfer.

Embryo collection is performed by using transcervical uterine lavage (Figure 5.20-1). After placing the mare in stocks, the perineal area is cleaned with a mild detergent, rinsed thoroughly with clean water, and dried. The operator then places a sterile plastic sleeve over his or her arm, applies sterile lubricant, and introduces a sterile balloon-tipped catheter into the mare's vagina. This author uses an 80-cm silicone catheter (VEUF, Bivona, Gary, Ind.) that has an inside diameter of 8.0 mm (French size 33); however, other styles of flushing catheters are available. After the catheter has entered the vagina, the instrument is passed through the cervix into the uterine body, and the balloon-cuff is inflated with approximately 80 ml of air or sterile saline and is pulled back against the internal cervical os to prevent loss of fluid. Once the catheter is seated appropriately, the uterus is flushed three to four times with warm (30°-35° C) flush medium.

The most widely used flush medium has been Dulbecco's phosphate buffered saline, which contains 1% (v/v) fetal or newborn calf serum, penicillin (100 U/ml), and streptomycin (100 µg/ml). More recently, however, many practitioners have begun to use a zwitterion-buffered flush medium that contains antibiotics and bovine serum albumin (emCare Complete Flush Solution, Professional Embryo Transfer Supply, Canton, Tex.) or polyvinyl alcohol (Vigro Complete Flush Solution, AB



**Figure 5.20-1** Method of transcervical uterine lavage for recovery of embryos. (Modified from Aguilar J, Woods GL: Embryo transfer in horses: indications, technique and expected outcomes. In Youngquist R (ed): *Current Therapy in Large Animal Theriogenology*, pp 208-213, Philadelphia, WB Saunders, 1997.)

Technology, Pullman, Wash.). Regardless of which medium is used, with the use of gravity flow the uterus is filled with 1 to 2 L of medium during each flush (4-8 L used during entire procedure). After filling the uterus, the fluid is allowed to flow back out through the catheter and is passed through a 0.75  $\mu$ m embryo filter. The embryo filter must not overflow or run dry; filters are available that are designed to prevent both from occurring. The fluid passing through the filter is collected to monitor its recovery. After the first flush, the veterinarian massages the uterus per rectum during subsequent flushes. This massage may aid suspension of the embryo(s) in the medium and enhance fluid recovery. The majority (>90%) of fluid infused into the uterus should be recovered and should be free of cellular debris or blood. Recovery of "cloudy" fluid indicates the mare had an active endometritis at the time of the embryo recovery, and warrants further diagnostic evaluation. When present, blood contamination is often associated with vigorous massage of the uterus and/or manipulation of the catheter.

At the completion of the flush, the embryo filter is emptied into a sterile search dish with grid and the filter is rinsed with approximately 50 ml of flush medium. The fluid is then examined for the embryo(s) with use of a stereo-microscope at approximately 15 $\times$  magnification. Large embryos ( $\geq$ day 8 postovulation) are generally visible with the naked eye. When an embryo is identified, it is washed by sequential transfer through several (3-10) 1 ml drops of holding medium, which consists of an enriched formulation of flush medium. After the washing, the embryo is placed into a small Petri dish that contains the same medium. The embryo is then examined at high magnification (40-80 $\times$ ) and graded on a scale of 1 (excellent) to 4 (poor). Embryos can be handled with a 0.25- or 0.5-ml semen-freezing straw, 25- $\mu$ l glass capillary pipette, or other suitable instrument attached to an appropriate sy-

ringe. Each time an embryo is drawn into a handling instrument, the medium that contains the embryo should be surrounded on each side by an air bubble and blank medium. This setup prevents the embryo from being accidentally pulled out of the instrument should the tip make contact with something absorbent.

Once embryos are placed into the holding medium, they should be expeditiously transferred into an appropriate recipient mare or processed for storage (discussed below). While awaiting immediate transfer to a recipient or processing for storage, equine embryos are quite tolerant of temperatures between room temperature (25 $^{\circ}$  C) and body temperature (37 $^{\circ}$  C); however, efforts should be made to prevent rapid or extreme changes in temperature and to minimize the length of time the embryos are maintained in holding medium.

As mentioned previously, unfertilized oocytes are retained in the oviduct where they degenerate over a period of several months; therefore they are usually not recovered during an embryo collection attempt. Occasionally, however, one or more old degenerating unfertilized oocytes from previous estrous cycles will be recovered during an embryo collection attempt. These old degenerating oocytes are invariably oval and/or flattened, which gives them a "football-shaped" or "pancake-shaped" appearance. The operator may need to use careful pipetting and/or gentle swirling of the embryo dish while viewing the dish through a stereo-microscope to discern this characteristic appearance. Although old degenerating oocytes are infrequently recovered from the uterus, they must be distinguished from viable embryos so that time and expense are not wasted in transfer of a nonviable oocyte to a recipient mare (or in shipping to an embryo transfer facility).

## EMBRYO STORAGE

Two options exist to store equine embryos. The short-term (<24 hours) method entails storage of embryos that are cooled to 5 $^{\circ}$  C in an Equitainer (Hamilton Research, South Hamilton, Mass.). The long-term (>24 hours) method involves storage of embryos that are frozen at -196 $^{\circ}$  C in liquid nitrogen. Of these two options, short-term storage procedures are currently more practical and widely used for the transport of embryos in commercial embryo transfer programs. Embryos are cooled (and transported) in Ham's F-10 culture medium. Before use, the Ham's F-10 medium must be buffered by diffusing a mixture of 90% N<sub>2</sub>, 5% O<sub>2</sub>, and 5% CO<sub>2</sub> medical-grade compressed gas through the medium for 3 to 5 minutes, after which it is supplemented with 10% (v/v) fetal or newborn calf serum, penicillin (100 U/ml), and streptomycin (100  $\mu$ g/ml). Because Ham's F-10 medium must be "gassed" before use, an appropriate compressed gas cylinder and regulator are necessary. Therefore many practitioners choose to have the receiving embryo transfer facility provide Ham's F-10 as part of an embryo shipping kit. However, once Ham's F-10 has been prepared for use it has a limited shelf-life that requires the medium to be sent by express delivery for receipt by the practitioner within 24 hours before the scheduled embryo collection. Unfortunately, the expense associated with the preparation and shipment of the Ham's F-10 to the practitioner is wasted if no embryo is recovered,

because the Ham's F-10 cannot be stored for future use. Because of the need for specialized equipment for processing the Ham's F-10 and its limited shelf-life, the use of other media for cooling and storing equine embryos is being investigated.

To package an embryo in Ham's F-10, the prepared medium is filter-sterilized into a 5-ml plastic "snap-cap" tube, with a small air gap left at the top of the tube. The embryo is then carefully transferred into the medium, the cap is securely snapped onto the tube, and the tube is wrapped with parafilm (American National Can, Menasha, Wis.). A 50-ml centrifuge tube is then filled with Ham's F-10 medium (unfiltered), and the 5-ml tube containing the embryo is placed into the 50-ml centrifuge tube. The cap of the 50-ml centrifuge tube is closed with as much air eliminated as possible, and it is wrapped with parafilm. The packaged embryo is then placed into an Equitainer that passively cools the embryo to 5° C. Under those conditions, embryos can remain viable for at least 24 hours, which allows them to be transported by commercial airline or priority overnight delivery to an embryo transfer facility where the embryo is transferred into a suitable recipient mare. Extensive use of cooled embryos in commercial embryo transfer programs during the past 10 years has demonstrated that pregnancy rates achieved with cooled embryos are equivalent to those obtained with embryos transferred immediately after collection.

### Cryopreservation

In contrast to cooling embryos in Ham's F-10 medium, which allows storage for as long as 24 hours, embryos that are frozen in liquid nitrogen can be stored indefinitely. The ability to store frozen embryos indefinitely provides the three following advantages:

1. Embryos can be recovered from a donor mare regardless of whether a suitable recipient mare is available, because the embryo can be frozen and then thawed and transferred to a recipient mare at a later date.
2. Embryos can be shipped internationally, which cannot be accomplished with cooled embryos.
3. Embryos can be "banked" as an "insurance policy" against the untimely death of a mare.

Embryos are exposed to extremely harsh conditions during the freezing and thawing process; therefore, specialized cryopreservation procedures are used to help minimize damage to embryos during these events. Current cryopreservation procedures fall into two categories—conventional methods and vitrification. With conventional cryopreservation methods, most of the intracellular water must be removed from the embryonic cells before freezing occurs; if this is not accomplished, large intracellular ice crystals form that cause severe physical damage to cells and/or cell death. Water is osmotically removed from cells through cooling/freezing in a carefully controlled manner. When embryos are cooled/frozen while suspended in a physiologic medium, the first water to freeze is located in the extracellular space. The ice crystals that begin to form in the extracellular space are composed of relatively pure water, which leaves the unfrozen liquid in the extracellu-

lar space higher in solute concentration (hyperosmotic). The hyperosmotic fluid in the extracellular space then draws water out of the embryonic cells dehydrating them. If embryos are cooled/frozen too rapidly, water freezes within the cells before it is osmotically removed and cell damage/death occurs. Conversely, if embryos are cooled/frozen too slowly the cells are exposed to extremely high solute concentrations, which also results in cell damage and/or death. Therefore the cooling/freezing rate must be carefully controlled to optimize the amount of cellular dehydration that occurs during the freezing process. Precise control of the cooling/freezing rate is achieved with a programmable freezing instrument.

To maximize cell survival during cryopreservation procedures, cryoprotectants are added to the freezing medium. Two classes of cryoprotectants exist—permeating, intracellular cryoprotectants such as glycerol, dimethyl sulfoxide (DMSO), and ethylene glycol and nonpermeating, extracellular cryoprotectants such as sucrose and serum albumin. In general both permeating and nonpermeating cryoprotectants are used; however, the permeating cryoprotectants are the most important. The mechanism of action of the cryoprotectants is not known, but it may be related to their lowering of the freezing temperature of the medium and/or their effects on the physical structure of ice.

Although permeating cryoprotectants are necessary for conventional cryopreservation procedures, the presence of the permeating cryoprotectant(s) within the embryonic cells presents a problem during the thawing process. If embryos are thawed and then placed directly into a cryoprotectant-free medium (or body fluids), water will rush into the embryonic cells to osmotically dilute the cryoprotectant before the cryoprotectant can diffuse out of the cells. This influx of water occurs because cells are much more permeable to water than to most cryoprotectants. The rapid entry of water can damage cells by causing rapid osmotic swelling to the point that cell lysis may occur. Two general approaches to overcoming this problem—dilution of the permeating cryoprotectant in relatively small steps or placement of the embryo into a medium that contains a relatively high concentration of a nonpermeating extracellular cryoprotectant. Both methods allow the permeating cryoprotectant to slowly equilibrate without an excessive influx of water into the embryonic cells.

### Vitrification

In contrast to conventional cryopreservation procedures, vitrification involves the use of extremely high concentrations of permeating cryoprotectants that cause both intracellular and extracellular fluids to become more viscous when cooling/freezing occurs, rather than forming ice crystals. The absence of damaging ice crystals is a major advantage of this technique. Vitrification also obviates the need to cool embryos slowly thereby eliminating the need for expensive programmable freezing instruments, because packaged embryos can be plunged directly into liquid nitrogen for freezing. The primary disadvantage of vitrification is that the high concentration of cryoprotectant used can be toxic to embryos. The veterinarian can minimize the potential for toxicity by shortening the time of exposure to cryoprotectant before freezing, adding cryo-

protectant at cold temperatures, and removing the cryoprotectant rapidly after thawing.

Currently, conventional cryopreservation procedures utilizing glycerol as the primary cryoprotectant appear most suitable for long-term storage of equine embryos. However, the size of the embryo has a profound effect on the pregnancy rate achieved after cryopreservation. It has been clearly demonstrated that small ( $\leq 250 \mu\text{m}$ ), early-stage embryos (late morula to early blastocyst) survive cryopreservation better than larger ( $\geq 300 \mu\text{m}$ ) more advanced embryos (blastocyst to expanded blastocyst). The reason for the influence of embryonic size and/or stage of development on tolerance of cryopreservation procedures by equine embryos is not known. To obtain embryos in the optimal size range, embryos must be collected on day 6 postovulation. Unfortunately some embryos may still be in the oviduct, which precludes recovery, whereas some embryos will already exceed  $250 \mu\text{m}$  in diameter. Therefore obtaining embryos of the appropriate size/stage for cryopreservation purposes is problematic. Embryos that are  $250 \mu\text{m}$  or less in diameter when frozen by using conventional cryopreservation procedures with use of glycerol achieve pregnancy rates close to 50% after transfer, whereas embryos that are  $300 \mu\text{m}$  or more in diameter achieve very low pregnancy rates after transfer. Further work is clearly necessary to optimize the success of cryopreservation procedures for equine embryos. It is unlikely that long-term storage of frozen equine embryos will become widely adopted until procedures are developed that allow survival of larger, more advanced embryos (i.e., at days 7 and 8 postovulation).

## EMBRYO TRANSFER

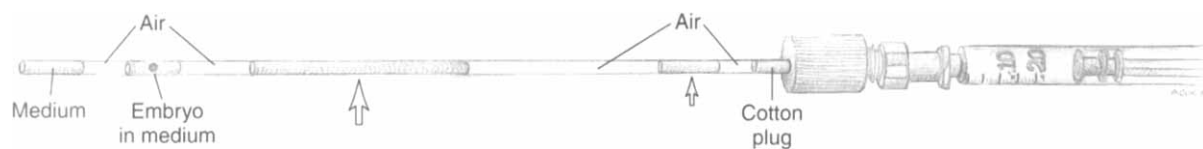
Regardless of whether embryos are transferred immediately after recovery or stored (cooled or frozen) before transfer, the transfer procedure can be performed surgically or nonsurgically. Surgical transfer has provided the highest pregnancy rates and most consistent results to date, with pregnancy rates of approximately 70% to 75% 1 week after transfer of fresh or cooled embryos. However, the use of nonsurgical transfer is rapidly becoming more widespread and the success rates can be equal to, or greater than, those obtained with surgical transfer.

Surgical embryo transfer is performed as a standing flank laparotomy with use of appropriate sedation/tranquilization in conjunction with local anesthesia. With standard surgical techniques the uterine horn is exteriorized through a flank incision and is punctured with a cutting-edge suture needle. The embryo, contained within a small amount of medium ( $<250 \mu\text{l}$ ) in a sterile embryo handling instrument, is then deposited through the puncture wound into the uterine lumen. After the transfer, the veterinarian replaces the uterine horn into the abdomen without closing the puncture wound in the uterine wall, and the abdominal incision is closed using standard technique. Because of its intrauterine mobility, the equine embryo can be transferred into the uterine horn ipsilateral or contralateral to the side of ovulation.

Nonsurgical embryo transfer can be performed with one of the following instruments:

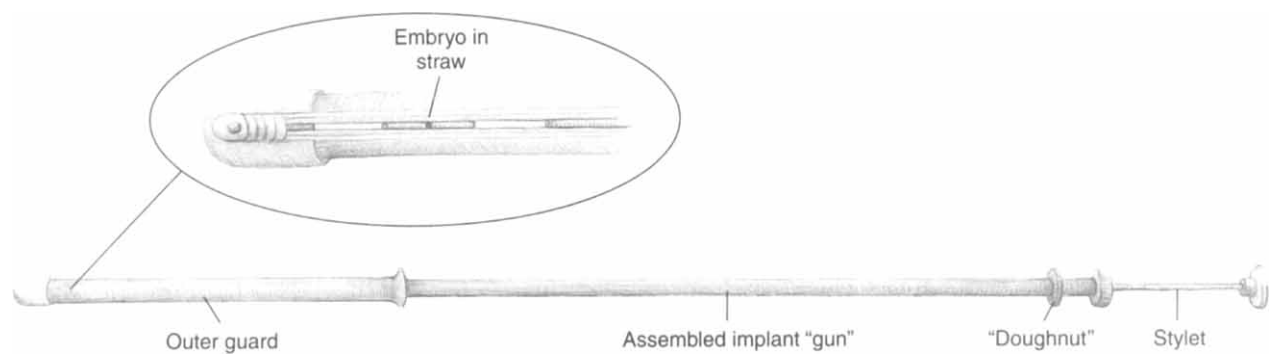
1. A standard artificial insemination pipette
2. A 25-inch disposable plastic implant "gun" that accepts a 0.5-ml semen straw (product #04149; Veterinary Concepts, Spring Valley, Wis.)
3. A 21-inch reusable stainless steel deep-chamber implant "gun" that accepts a 0.25-ml semen straw (product #04805; Veterinary Concepts)

This author prefers the reusable 0.25-ml, deep-chamber implant gun that is illustrated in Figures 5.20-2 through 5.20-4. The embryo is loaded into a sterile 0.25-ml semen straw that is plugged on one end (see Figure 5.20-2). The loaded straw is then placed into the distal end of the implant gun and a metallic-tipped sterile sheath is placed over the gun and secured in place with a plastic "doughnut" at the proximal end (see Figure 5.20-3). An outer sterile guard is then placed over the metallic-tipped sheath before the transfer procedure is formed (see Figure 5.20-3). For a nonsurgical transfer procedure the recipient mare is placed in stocks and sedated, and the perineal area is cleaned and prepared with standard procedures. The operator places a sterile plastic sleeve over his or her arm, and a sterile surgeon's glove is placed over the plastic sleeve. A small amount of sterile lubricant is placed on the back of the operator's hand and applied to the vulva. The tip of the transfer instrument (covered by the outer

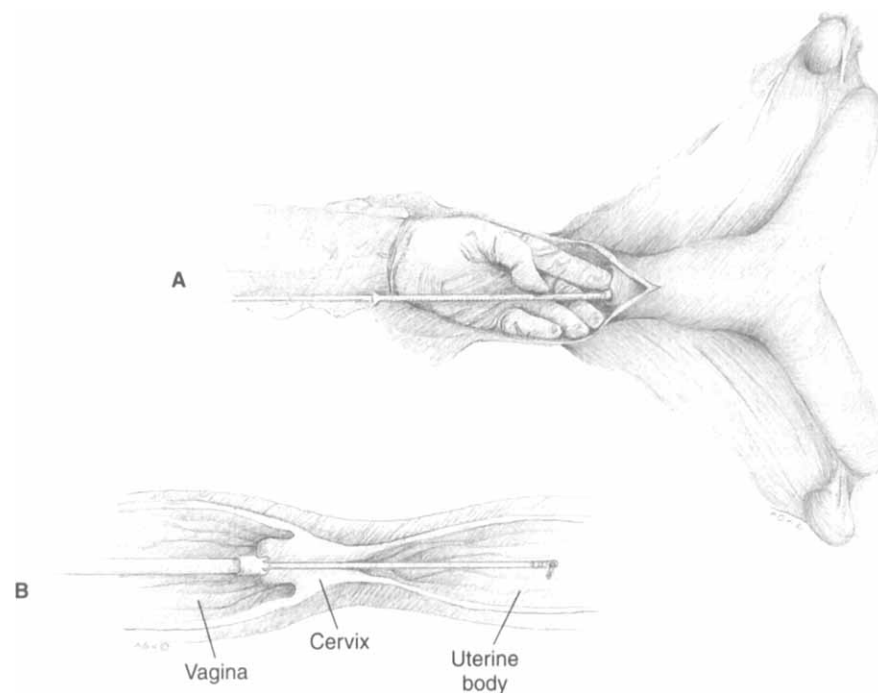


**Figure 5.20-2** Embryo being loaded into a sterile 0.25-ml semen straw. The straw is attached to a tuberculin syringe with a ureteral catheter connector (product #V-050010, Cook Urological, Bloomington, Ind.) that allows medium and/or air to be drawn into the straw. Within the medium the embryo is "sandwiched" between air and fluid columns. The large fluid column to the right of the embryo (*large arrow*) will be the "push" column of medium that will force the embryo out of the straw when the stylet of the implant gun is advanced through the straw. The small column of medium at the far right end of the straw (*small arrow*) will be used to wet the cotton plug in the end of the straw before it is detached from the syringe. This method provides an air-tight seal that prevents the contents of the straw from moving until the stylet is advanced through the straw. After the cotton plug has been wetted, the straw is detached from the syringe and placed into the chamber of the implant gun.





**Figure 5.20-3** Completely assembled implant gun. The straw that contains the embryo is locked in the chamber of the gun by the metallic-tipped sheath shown in the cut-away view (*inset*), which is held in place by a “doughnut” at the proximal end of the gun. The metallic-tipped sheath is covered by a rigid outer sterile guard (other styles of outer guard are available).



**Figure 5.20-4** Placement of the implant gun into the uterine lumen and deposition of the embryo. **A**, A gloved hand is used to guide the outer sterile guard approximately 0.5 cm into the external cervical os. Once the outer guard is positioned into the external cervical os, the outer guard is stabilized and the implant gun (covered by the metallic-tipped sheath) is passed through the outer guard and advanced through the cervix into the uterine lumen. **B**, After the tip of the implant gun is positioned in the uterine lumen, the stylet is advanced through the gun, which expels the embryo into the uterine lumen. (Modified from Pickett BW, Voss JL, Squires EL et al: Mechanics of artificial insemination. In Collection, Preparation and Insemination of Stallion Semen: Animal Reproduction and Biotechnology Laboratory, Bulletin No. 10, pp 55-71, Fort Collins, Colo, Colorado State University, 2000.)

guard) is placed in the palm of the hand and protected by placing the operator's thumb over the tip. The instrument is introduced into the vagina, and the tip of the outer guard is introduced approximately 0.5 cm into the external cervical os, at which point the instrument is advanced through the outer guard and passed through the

cervix into the uterine lumen (Figure 5.20-4). The embryo can be deposited in the uterine body or in one of the uterine horns; to deposit the embryo in the uterine horn, the tip of the instrument is guided into the horn with transectal manipulation.

No evidence currently exists that the site of embryo

placement (uterine body versus horn) during nonsurgical transfer influences the outcome. Once the transfer instrument is positioned appropriately, the embryo is expelled as the transfer instrument is withdrawn slightly so that the tip is not pushed up against the endometrium as the embryo is deposited into the uterus.

## SUMMARY

Embryo transfer is a valuable assisted reproductive technique in the mare. Although the use of embryo transfer in commercial breeding programs was initially hampered by the need to provide suitable recipient mares at the site of embryo collection, or transport donor mares to a centralized embryo transfer facility, the development of methods that allow short-term storage and transportation of embryos eliminates the need for maintaining recipients on site. These new methods in addition to the fact that the materials necessary for embryo collection and transport are well suited to a field setting, enables more veterinarians to provide embryo transfer service to their clientele who wish to use this technology.

Although embryo transfer provides a means to obtain pregnancies from some mares that might not otherwise be capable of producing offspring, some mares cannot provide embryos for transfer. Mares in which embryo transfer may not be successful include those with ovula-

tory failure, chronic endometritis, or anatomic problems (e.g., cervical adhesions). However, these mares could be used as oocyte donors and continue to produce foals through newer assisted reproductive techniques such as oocyte transfer, *in vitro* fertilization, or intracytoplasmic sperm injection. These techniques are currently being developed for use in horses, and are discussed elsewhere in this volume.

## Supplemental Readings

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# CHAPTER 5.21

## Oocyte Transfer

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Fort Collins, Colorado

Oocyte transfer is the placement of a donor's oocyte into the oviduct of a recipient. The recipient can be inseminated within the uterus or within the oviduct. Placement of the oocyte and sperm within the recipient's oviduct is more accurately termed *gamete intrafallopian transfer* (GIFT).

The first successful oocyte transfer was done in 1989; however, the technique was not used for commercial transfers until the late 1990s. Oocyte transfer is currently used to produce offspring in subfertile mares in which embryo transfer is not successful because of various reproductive problems. These problems include ovulatory failure, oviductal blockage, recurrent or severe uterine infections, and cervical tears or scarring. In some cases, the cause of reproductive failure cannot be diagnosed; however, oocyte transfer can be successful.

## SYNCHRONIZATION OF DONORS AND RECIPIENTS

Oocytes are collected from preovulatory follicles between 24 and 36 hours after the administration of human chorionic gonadotropin (hCG; 1500-2500 IU, IV) to a donor mare or between 0 and 14 hours before anticipated ovulation. Criteria for hCG administration are as follows:

- Follicles greater than 35 mm in diameter
- Relaxed cervical and uterine tone
- Uterine edema or estrous behavior present for 2 or more days

Some mares, especially older mares, do not consistently respond to hCG. In these cases, this author uses a combination of the gonadotropin-releasing hormone (GnRH) analog, deslorelin acetate (2.1 mg implant; Ovuplant),

placement (uterine body versus horn) during nonsurgical transfer influences the outcome. Once the transfer instrument is positioned appropriately, the embryo is expelled as the transfer instrument is withdrawn slightly so that the tip is not pushed up against the endometrium as the embryo is deposited into the uterus.

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- Uterine edema or estrous behavior present for 2 or more days

Some mares, especially older mares, do not consistently respond to hCG. In these cases, this author uses a combination of the gonadotropin-releasing hormone (GnRH) analog, deslorelin acetate (2.1 mg implant; Ovuplant),

followed by an injection of hCG (2000 IU, IV) between 4 and 5 hours later.

Oocytes collected 36 hours after hCG administration to the donor are transferred immediately into a recipient's oviduct. Oocytes collected 24 hours after drug administration to the donor are cultured *in vitro* for 12 to 16 hours before transfer. The advantage of collection of oocytes between 32 and 36 hours after hCG administration to the donor is that the oocytes do not require culture *in vitro*. However, donors could ovulate follicles before oocytes are collected. The collection and culture of oocytes at 24 hours after hCG administration to the donor are often easier to schedule; the oocyte can be collected in the afternoon and transferred the next morning. This method requires expensive equipment and training for tissue culture, however. In a modification of these procedures, oocytes are collected 24 hours after hCG and immediately transferred into the recipient's oviduct to allow maturation to complete within the oviduct. With this latter method, recipients are inseminated 16 hours after transfer.

## OOCYTE COLLECTION

Oocytes are usually collected by one of two methods. In one method, the ovary is held per rectum against the ipsilateral flank of the mare. A puncture is made through the skin and a trocar is advanced into the abdominal cavity. The ovary is held against the end of the trocar while a needle is advanced through the trocar and into the follicular antrum.

In this author's laboratory oocytes are collected by using transvaginal, ultrasound-guided follicular aspirations. For this procedure, a linear or curvilinear ultrasound transducer is used with the transducer housed in a casing with a needle guide. Before the procedure, the rectum is evacuated and the vulvar area is cleaned. The mare is sedated (xylazine HCl, 0.4 mg/kg, and butorphanol tartrate, 0.01 mg/kg, IV) and a substance to relax the rectum (propantheline bromide, 0.04 mg/kg, IV) is administered. A twitch is applied. The probe is covered with a nontoxic lubricant and placed within the anterior vagina lateral to the posterior cervix and ipsilateral to the follicle to be aspirated. The follicle is positioned per rectum and stabilized with the apex of the follicle juxtaposed to the needle guide. A needle is advanced through the needle guide to puncture the vaginal and follicular walls. In this author's laboratory, a 12-gauge, double-lumen needle is used (Cook Veterinary Products, Spencer, Ind.). The follicular fluid is aspirated from the follicle by using a pump set at a pressure of  $-150$  mm Hg. After removal of follicular fluid, the lumen of the follicle is lavaged with 50 to 100 ml of flush (typically modified Dulbecco's phosphate-buffered solution or Emcare [ICP, Auckland, New Zealand]) that contains fetal calf serum (1%) or bovine serum albumin (0.4%) and heparin (10 IU/ml).

Equipment used to handle the oocyte is warmed to  $38.5^{\circ}\text{C}$  before use because the oocyte is sensitive to temperature changes. On collection, the follicular aspirate and flush are poured into large search dishes and examined under a dissecting microscope to locate the oocyte. Aspirations of preovulatory follicles are often bloody because the follicle has increased vascularity as ovulation ap-

proaches. The oocyte is approximately  $100\text{ }\mu\text{m}$  in diameter and is surrounded by a large mass of nurse cells—the cumulus complex. Cumulus cells, or the corona radiata, appear as a ring surrounding the oocyte. When the oocyte matures, the cumulus complex becomes less distinct. The corona radiata appears clear in the bloody flush solution and can be observed by the naked eye.

## OOCYTE EVALUATION AND CULTURE

On collection, cumulus oocyte complexes (COC) are evaluated for cumulus expansion (graded from compact to fully expanded) and for signs of atresia. Oocytes are determined to be in a stage of atresia when the COC is clumped and/or sparse, the corona radiata is fully expanded, or when the ooplasm is shrunken and dark or severely mottled. Oocytes with a fully expanded cumulus (marked separation of cumulus cells with expansion of the corona radiata) are considered mature and are transferred as soon as possible into a recipient's oviduct. Oocytes with a moderately expanded cumulus complex (translucent COC with moderate separation of cumulus cells and incomplete expansion of corona radiata) are cultured before transfer. On occasion, the donor does not respond to hCG and the follicle does not begin to mature. Consequently, the granulosa cells that line the follicle are collected in small, compact sheets, and the oocyte is frequently not retrieved. If an immature (compact COC with little or no separation of cumulus cells) oocyte is collected, special culture conditions are required, including a maturation medium with additions of hormones and growth factors.

On identification and evaluation, the oocyte is washed and placed in a transfer or collection medium. A commonly used medium for the culture of maturing oocytes is tissue culture medium (TCM) 199 with additions of 10% fetal calf serum, 0.2 mM pyruvate, and 25 mg/ml gentamicin sulfate. A carbon dioxide ( $\text{CO}_2$ ) incubator must be used to establish the proper culture conditions of  $38.5^{\circ}\text{C}$  in an atmosphere of 5% or 6%  $\text{CO}_2$  and air.

## OOCYTE TRANSFER

Mares that will receive oocytes should be young (preferably 4-10 years of age) with a normal reproductive tract. Oocytes are transferred surgically; therefore, adequate exposure of the ovary is essential to facilitate transfers. Mares with short, thick flanks and short broad ligaments are not good candidates for recipients. Both cycling and noncycling mares have been used as oocyte recipients. When cyclic mares are used, they must be synchronized with the donor; thus, hCG is administered to the estrous donor and recipient at the same time of day. Before the mare can be used as a suitable recipient, her own oocyte must be aspirated. Anestrus and early transitional mares are suitable noncyclic recipients. During the breeding season, a high dose of a GnRH analog or injections of progesterone and estrogen (150 mg progesterone and 10 mg estradiol) can be administered to reduce follicular development in potential recipients. Noncyclic recipients are given injections of estradiol (2-5 mg daily for 3-7 days) before transfer and progesterone (150-200 mg daily) after transfer. In mares

that are not having estrus cycles, pregnancies must be maintained through the use of exogenous progesterone.

Oocytes are transferred through a flank laparotomy into standing sedated mares. Recipients are placed in a stock and a presurgical sedative (xylazine HCl, 0.3 mg/kg, and butorphanol tartrate, 0.01 mg/kg, IV) is administered. The surgical area is clipped, scrubbed, and blocked with a 2% lidocaine solution. Immediately before surgery, additional sedation is administered (detomidine HCl, 9 mg/kg, and butorphanol tartrate, 0.01 mg/kg, IV). An incision is made through the skin approximately midway between the last rib and tuber coxae, and the muscle layers are separated through a grid approach. The ovary and oviduct are exteriorized through the incision. The oocyte is pulled into a fire-polished, glass pipette, and the pipette is carefully threaded into the infundibular os of the oviduct and advanced approximately 3 cm. The oocyte is transferred with less than 0.05 ml of medium.

### INSEMINATION OF RECIPIENTS

In a commercial oocyte transfer program, use of stallions with good fertility is essential. Cooled and transported semen is often provided. When fresh semen from fertile stallions and oocytes from young mares was used in different experiments, insemination of the recipient only before (12 hours) or only after (2 hours) oocyte transfers resulted in embryo development rates of 82% (9/11) and 57% (8/14), respectively. In a commercial oocyte program, mares were older with histories of reproductive failure and cooled semen from numerous stallions of variable fertility was used. Pregnancy rates when recipients were inseminated before or before and after oocyte transfer were significantly higher than when recipients were only inseminated after transfer (18/45, 40%; 27/53, 51% and 0/10, respectively). These results suggest that the insemination of a recipient before transfer with  $5 \times 10^8$  to  $1 \times 10^9$  progressively motile sperm from a fertile stallion is sufficient. However, if fertility of the stallion is not optimal, insemination of the recipient before and after transfer may be beneficial.

After insemination and transfer, the recipient's uterus is examined by ultrasonography to detect intrauterine fluid

collections. The uterine response to insemination often appears to be more severe when recipients are inseminated after transfer than when they are inseminated only before transfer. The uterus is evaluated and treated once or twice daily until no fluid is imaged. Recipients with accumulations of intrauterine fluid are treated similar to ovulating mares, with administration of oxytocin or prostaglandins to stimulate uterine contractions or with uterine lavage and infusion.

### FUTURE OF OOCYTE TRANSFER

Oocyte transfer has proved to be a valuable method of obtaining pregnancies from mares that cannot carry their own foal or produce embryos for transfer. Because the mare does not have to ovulate or provide a suitable environment for fertilization or embryo development, the oocyte donor is only required to develop a preovulatory follicle with a viable oocyte.

The transfer of oocytes and a low number of sperm (200,000 motile sperm) into the oviduct of recipients has been successful. Pregnancies could be produced with GIFT when sperm numbers are limited, such as from subfertile stallions and from sex-selected or frozen sperm.

Through the use of this technique at this author's laboratory, pregnancies have been recently produced from oocytes that were frozen and thawed and from oocytes that were collected from the excised and shipped ovaries of dead mares. These advances provide excellent methods to preserve the genetics of valuable mares.

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## CHAPTER 5.22

# Determination of Fetal Gender

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*Lexington, Kentucky*

Fetal gender determination has been incorporated into the management programs of many breeding farms. Depending on the sire or the dam, the fetal gender may affect the value of the fetus and therefore influence the value of the pregnant mare. This knowledge could change various management decisions such as appraisals, foaling location, sales' reserves, insurance coverage, collateral limits for loans, mating lists for the next year, and buy/sell decisions.

Table 5.22-1 shows what to expect at the different stages of fetal development. Images in different ultrasound planes are shown in Figures 5.22-1 through 5.22-3. The basis for sex determination when the fetus is between 55 and 90 days' gestation is the location of the genital tubercle—a bilobulated hyperechoic structure 2 to 3 mm in length. This structure resembles a brightly colored “equals” symbol (see Figure 5.22-2, G), and is the precursor for the penis in the male and the clitoris in the female. The tubercle develops between the hind legs on the ventral midline in both sexes and at approximately day 53 or 54 of gestation appears to begin migrating toward the umbilical cord in the male and toward the anus in the female. Location of the tubercle between 55 and 90 days' gestation enables the practitioner to determine the gender.

When the fetus has reached 55 to 80 days' gestation, a veterinarian should be able to make a gender diagnosis 95% of the time with one examination. The accuracy of fetal sexing should reach 99%, and the time required to make the determination should range from a few seconds to 5 minutes depending on the experience of the clinician. At 80 to 90 days the fetus is temporarily difficult to reach due to the positioning of the uterus in the posterior abdomen. At approximately 80 days the fluid of the pregnancy pulls the uterus over the rim of the pelvis. The fetus is small, falls to the ventral portion of the uterus, and is difficult to reach. As the fetus grows, the uterus actually elevates more in the abdominal cavity and the fetus becomes easier to reach and view (Figure 5.22-4). After 90 days' gestation, the tubercle becomes less distinct and more difficult to see. Therefore, the clinician must rely on developing external genitalia—in the female, the mammary gland, teats, and clitoris (see Figures 5.22-1, C and D, and 5.22-2, E), and in the male, the penis and prepuce (see Figures 5.22-2, H, 5.22-3, D, and 5.22-3, E)—to make the gender diagnosis. Consistent differentiation between male and female gonads at differing stages of gestation is difficult (Figure 5.22-5). Consequently, gonads are used only for the reinforcement of a diagnosis, not for the diagnosis itself. At 90 to 150 days of gestation, a veterinarian should be able to formulate a highly accurate gender diagnosis 85% to 90% of the time. The diagnosis should re-

quire a few seconds to 10 minutes to perform, again, depending on the experience of the practitioner.

An attempt to sex the fetus should not last for more than 10 minutes per session on any one mare, because depending on the type of restraint used she may become fractious. No person or mare should experience injury during this elective procedure. If the mare becomes fractious, the veterinarian should stop and attempt the procedure on another day.

### MATERIALS

A high-quality ultrasound machine with a 5-MHz linear array rectal transducer (ALOKA 500 SSD [Aloka Co, Ltd., Wallingford, Conn.] or equivalent) is essential. If the overall gain, near gain, or far gain are set too high, the contrast between the fetus and background is less and the tubercle is more difficult to see. For optimal close eye level viewing, an ultrasound stand on wheels, subdued lighting for good screen visibility, and a hat are recommended. Video recordings or printers are helpful to verify the diagnosis and for record keeping.

Rectal palpation essentials include lubricant and sleeves and adequate restraint that might include a twitch, stocks, or tranquilizer. Depending on the situation, use of tranquilizers is acceptable, but this may cause the uterus to relax and drop away from the examiner and become more difficult to reach. This author uses xylazine (200 mg IV) mixed with butorphanol tartrate (10 mg). Propantheline bromide (30 mg IV) may be used to prevent rectal straining. Fly spray (if needed) will help to keep mare movement to a minimum.

### PROCEDURE

The procedure involves a thorough evacuation of the feces from the rectum to allow easy manipulation of the transducer. The clinician can determine the position of the fetus by scanning the entire fetus. The skull is a good anterior marker, the heart a good ventral marker, ribs coming off the vertebrae and the base of the tail are good dorsal markers, and the tail is a good posterior marker.

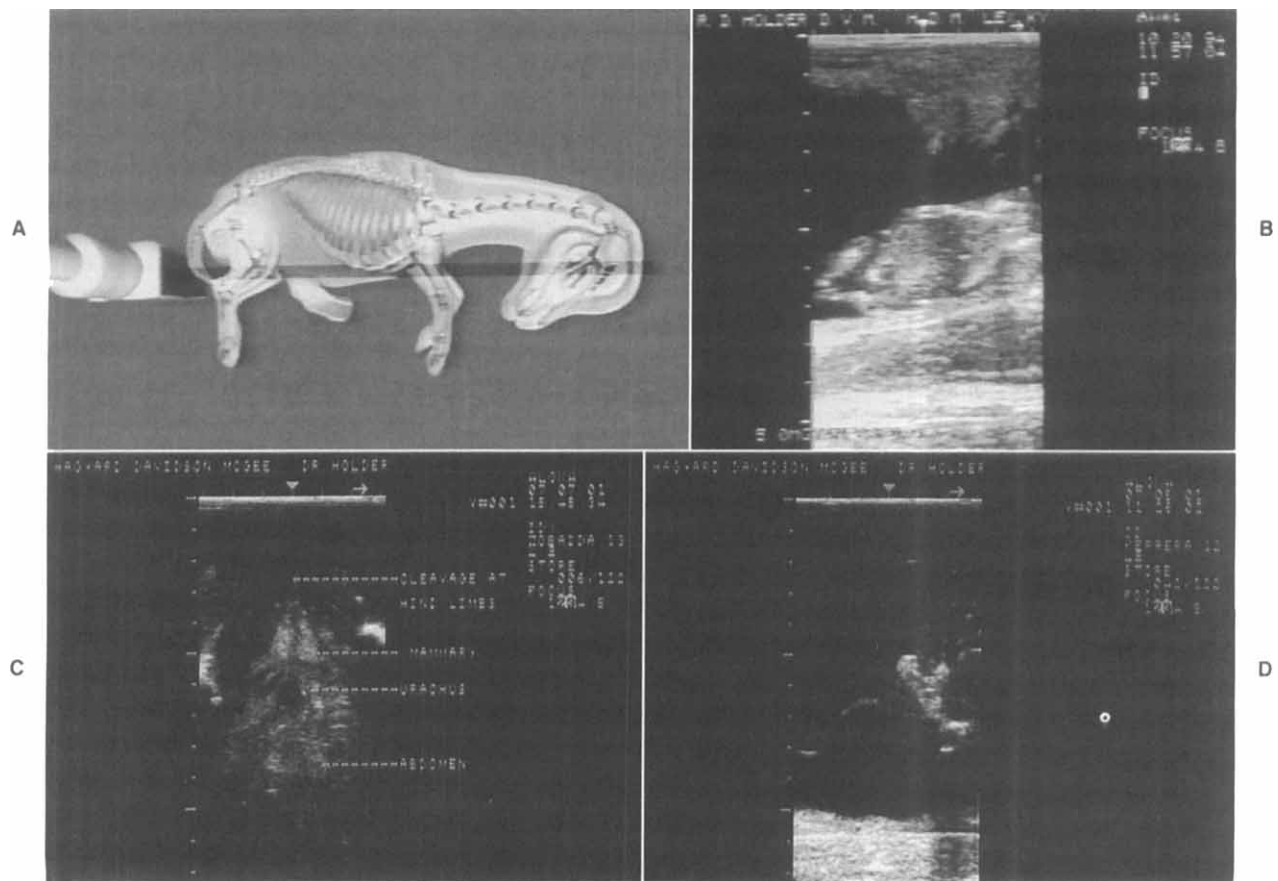
Once the position of the fetus has been determined, the veterinarian should proceed with the transducer to the posterior part of the fetus until the image of the latter has gone completely off the transducer (see Figures 5.22-1, A, 5.22-2, A, 5.22-2, F, and 5.22-3, A). The veterinarian should gradually ease back onto the fetus with the transducer and cut a plane perpendicular to the axis of the spine of the fetus (see Figure 5.22-2, A). A cross-section of the tailhead should be picked up on the dorsal aspect of the fetus. This cross-section will appear as a hyperechoic round mass with

*Text continued on p. 293*

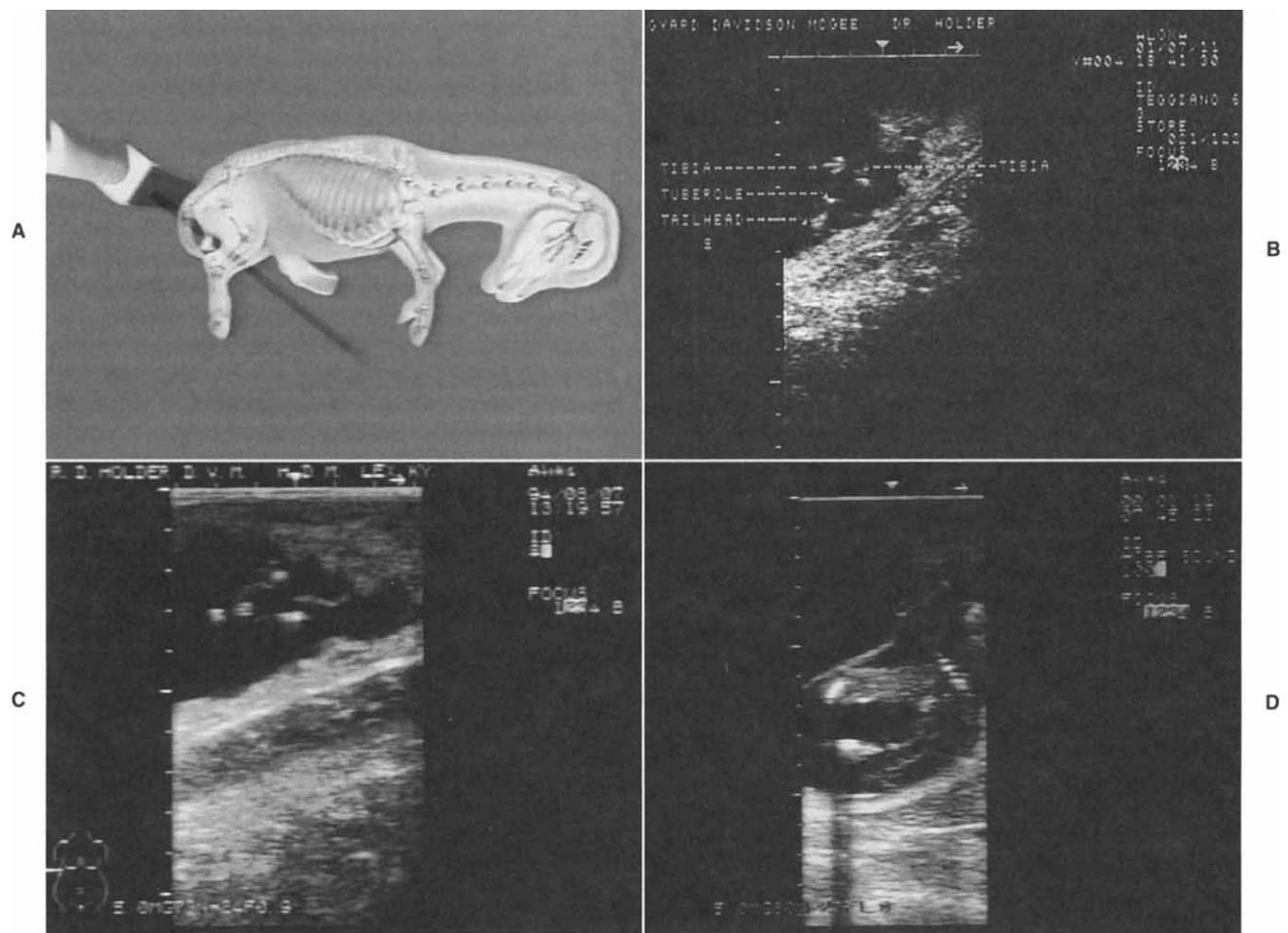
Table 5.22-1  
Development of Ultrasound Findings that Indicate Fetal Gender

Day(s)	Ultrasound Findings
55-60	Fetus is very small; genital tubercle is difficult to see; tubercle may or may not be fully migrated.
60-70	Ideal time for examination—fetal tubercle is distinct and fully migrated; fetus is accessible for viewing.
70-80	Fetus becomes more difficult to reach.
80-90	Most difficult time to view fetus—tubercle is less distinct; genitalia development is just beginning; fetus is frequently out of reach.
90-100	Fetus is generally accessible, but genitalia are not very well-developed.
100-110	Genitalia are becoming more evident.
110-120	Ideal time—genitalia is well-developed.
120-140	Genitalia is well-developed, but posterior of fetus may be difficult to access at times.
140-150*	At times the fetus has anterior presentation with posterior out of the examiner's reach.
150+	Usually the fetus has anterior presentation, and the posterior of the fetus is out of the examiner's reach.

\*Mares of 130 to 150 days' gestation that are classified as being "out of reach" should be viewed again for possible position changes.

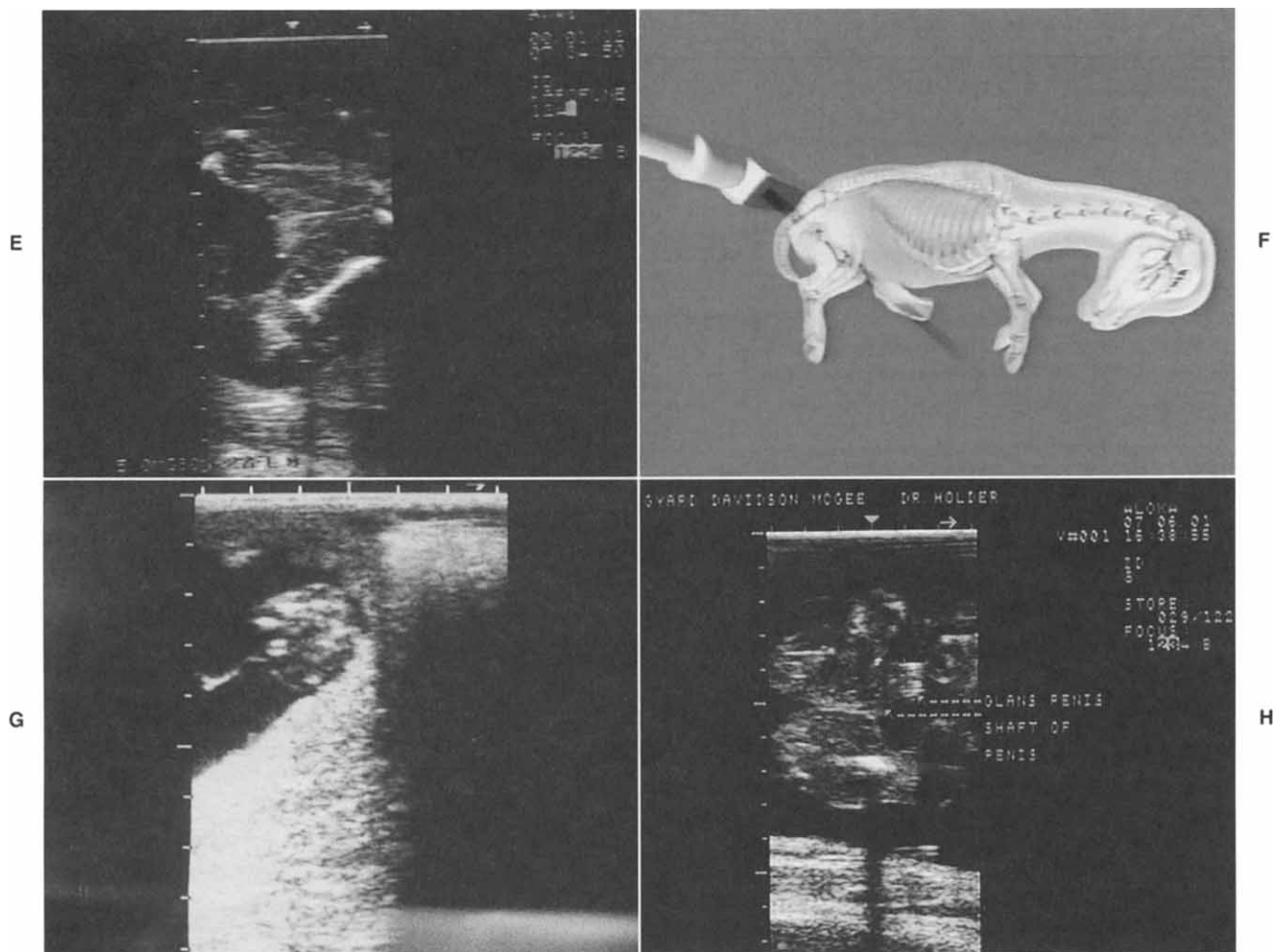


**Figure 5.22-1** Ultrasound cuts a frontal plane. **A**, Probe position for frontal plane imaging. **B**, Male fetus at 60 days. **C**, Female fetus of more than 100 days' gestation. **D**, Clitoris in cleavage of female fetus of more than 100 days' gestation.

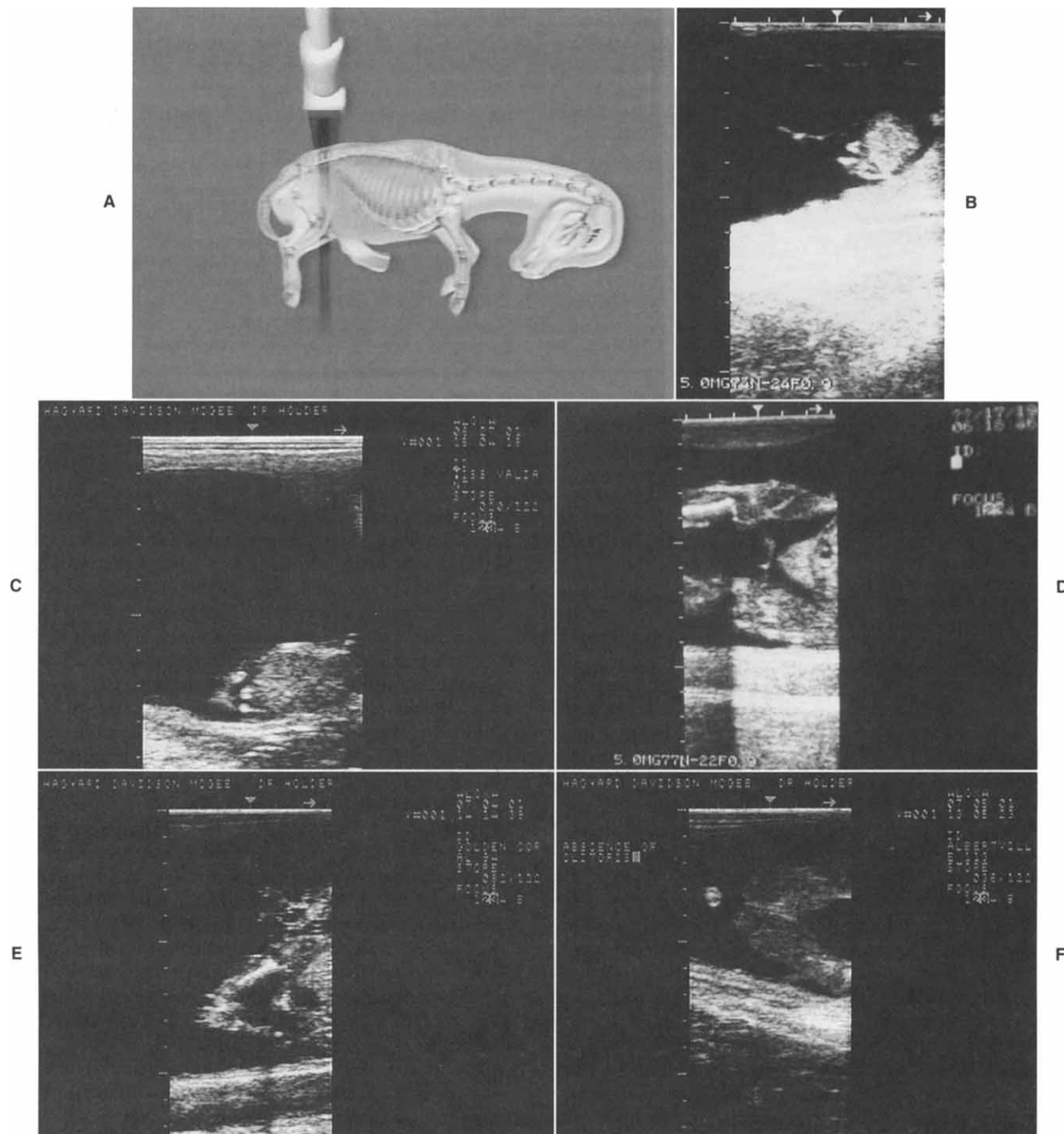


**Figure 5.22-2** Ultrasound cuts a plane perpendicular to the axis of the spine in the pelvic area (plane II). **A**, Probe position for imaging pelvic area. **B**, Tibia-tailhead (T-T) triangle at 60 days' gestation. **C**, Tibia-tailhead (T-T) triangle in 60-day female fetus. **D**, Female fetus at 90 days' gestation.

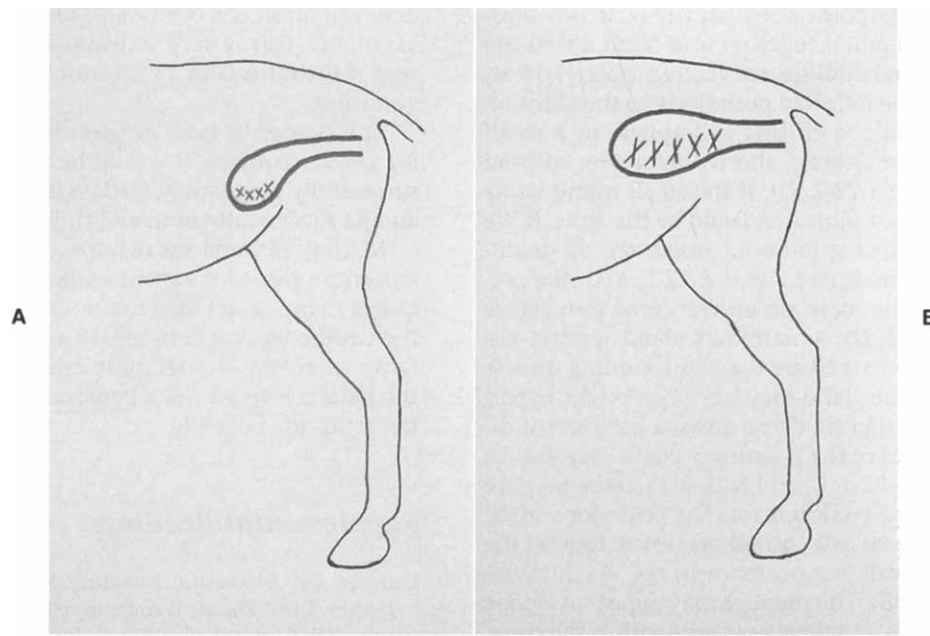




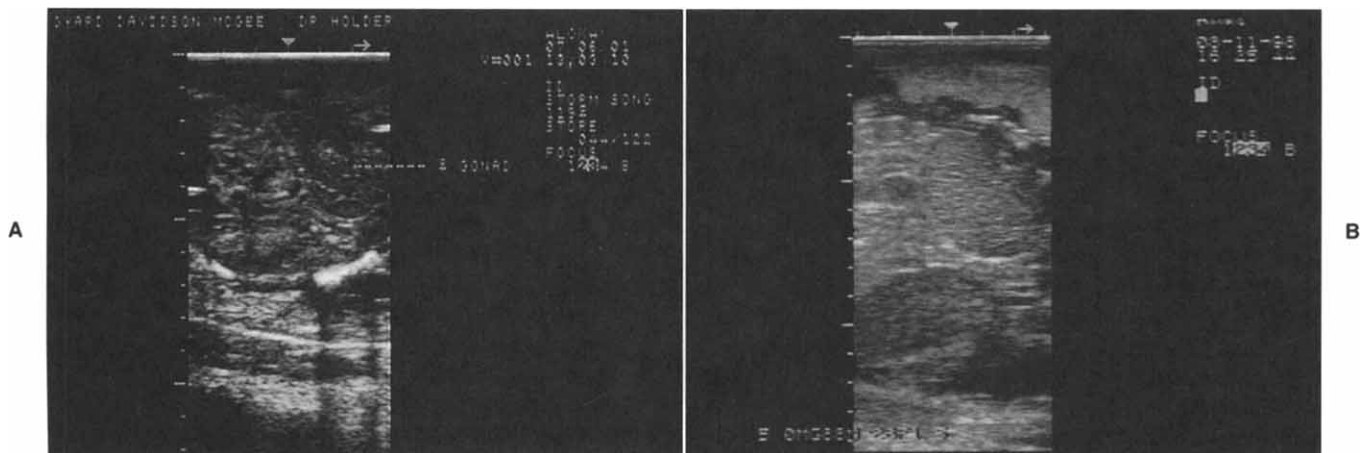
**Figure 5.22-2, cont'd** **E**, Mammary gland with teats in female fetus at 120 days' gestation. **F**, Male fetus. **G**, Male fetus at 60 days' gestation. **H**, Glans penis and shaft in male fetus of more than 100 days' gestation.



**Figure 5.22-3** Ultrasound cuts a plane perpendicular to the axis of the spine in the posterior abdominal area (plane III). **A**, Probe position for imaging posterior abdominal area. **B**, Prominent tubercle in 60-day male fetus. **C**, Portion of abdomen in 60-day male fetus. **D**, Prepuce cone in male fetus of more than 100 days' gestation. **E**, Glans penis in male fetus of more than 100 days' gestation. **F**, Posterior midline image of fetus of more than 100 days' gestation (plane III).



**Figure 5.22-4** Position of pregnant uterus at 80 (**A**) and 100 days (**B**) of gestation.



**Figure 5.22-5** Distinguishing features of male and female gonads. **A**, Female gonad has a slightly translucent central area. **B**, Male gonad has a homogenous central area.

very little muscle tissue around it. On the ventral aspect of the fetus, two tibias, which appear as hyperechoic round structures with no muscle mass, should be seen to form a triangle with the tailhead (see Figures 5.22-2, B, C, and D).

If the fetus is female, a hyperechoic tubercle will appear within the tibia-tailhead triangle with the tubercle slightly toward the tailhead. The female tubercle is difficult to consistently identify other than within the tibia-tailhead triangle (see Figure 5.22-2, B). If the fetus is a male, nothing will be seen within the tibia-tailhead triangle. If this is the case, the veterinarian should move the transducer gradually along the anterior aspect of the fetus, keeping the same perpendicular plane (plane II) to the axis of the spine of the fetus (see Figure 5.22-2, F). A hyperechoic structure resembling an "equals" symbol should be seen between the two tibias, which when the transducer is moved anteriorly become the stifles or femurs (see Figure 5.22-2, G). It is im-

portant to remember that tibias have no muscle mass around them but femurs do have muscle mass around them. When the transducer is moved further anteriorly, the large round abdomen will be seen. The male genital tubercle can often be seen on the outside ventral wall of the abdomen just posterior to the urachus, which is seen as a dark hole 4 to 5 mm in diameter (see Figures 5.22-3, B, C, D, and E). When the transducer is moved back and forth over the posterior area in this plane a tubercle is usually seen.

The male tubercle can also be readily seen from a frontal plane (Plane 1; see Figure 5.22-1, A). This plane exhibits the front legs, ventral abdomen, and hind legs with the tubercle appearing slightly anterior to a line drawn between the hind legs (usually femurs or stifles; see Figures 5.22-1, B, and 5.22-3, C).

After 90 days of gestation, the tubercle is less distinct. The veterinarian should proceed to the posterior aspect of

the fetus and find the point at which the posterior muscles of the buttocks come together and form a definite cleavage on the ventral midline (see Figure 5.22-3, *F*). Next, the cleavage should be followed posteriorly to the tailhead. If the fetus is a female, a clitoris will appear as a small round structure in the cleavage shortly before the tailhead is reached (see Figure 5.22-2, *D*). If the small round structure is too close to the tailhead, it could be the anus. If the midline or cleavage line is followed anteriorly, the mammary gland in the female (see Figure 5.22-2, *E*) or the prepuce and penis in the male are encountered (see Figure 5.22-2, *H*, and 5.22-3, *D*). A mammary gland appears as a triangular, slightly denser tissue than surrounding muscle tissue. Each half of the gland may have two bright hyperechoic teats and slightly dense areas; a translucent division between halves of the mammary gland may also be present (see Figures 5.22-1, *C*, and 5.22-2, *E*). If the prepuce is viewed from a cross-section across the posterior ventral abdomen, it will appear as a cone-shaped structure off the ventral abdominal wall just posterior to the urachus (see Figure 5.22-3, *D* and *E*). The prepuce may appear as a cone shaped structure with a hyperechoic area within the cone. The hyperechoic area is the penis itself (see Figure 5.22-3, *E*). Sometimes the shaft of the penis can be seen with a hyperechoic distal segment (see Figure 5.22-2, *H*).

When the fetus gets older, the genitalia become more developed and more easily differentiated from surrounding tissue. When the fetus develops, however, it becomes more difficult to access the posterior area. After day 150 of gestation, the fetus begins to have an anterior presentation that puts the posterior area out of reach. Also, because of its size the fetus is less apt to rotate the posterior part to a more accessible position. A fetal sex

determination has been made at 184 days on trans-rectal exam, but this is very unusual and possibly not a good sign if the fetus is in a posterior presentation this late in gestation.

This procedure is for gender identification only and not for gender control. It would be unusual to have a mare successfully pregnant at 60 days, terminate the pregnancy, and be successfully re-mated that season.

Mastery of these sex determination techniques by veterinarians provides a worthwhile service to clients but requires many hours of actual sonographic visualization of the equine fetus at between 55 and 150 days of gestation. Only when the sonographic cross-sectional anatomy of the fetus is learned will a consistent, accurate diagnosis of the fetus' sex be made.

### Supplemental Readings

- Ginther OJ: *Ultrasonic Imaging and Animal Reproduction: Horses*, Cross Plains, Wis, Equiservices Publishing, 1995.
- Ginther OJ, Curran S, Ginther M: *Fetal Gender Determination in Cattle and Horses* [instructional video], Cross Plains, Wis, Equiservices, 2002.
- Holder RD: *A Guide To Equine Fetal Sexing (55-150 days)* 2002 [instructional video], Wallingford, Conn, Aloka, 2002.
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## CHAPTER 5.23

# Interpretation of Peritoneal Fluid Changes in Peripartum Mares

GRANT S. FRAZER  
*Columbus, Ohio*

**A**bdominal discomfort in the peripartum mare poses a diagnostic dilemma for the equine clinician because of the difficulty in differentiating between normal uterine contractions and other sources of abdominal pain. When a periparturient mare displays abdominal discomfort she may be experiencing a reproductive problem including uterine torsion or rupture, vaginal tear involving the peritoneal cavity, hematoma of the uterine wall, or a uterine artery rupture. Possible lesions in other abdominal organs include rupture of the urinary bladder

or cecum, large colon impaction or torsion, or vascular compromise of a segment of bowel as a result of mesenteric rents or trauma. Several of these conditions can cause the affected mare to rapidly become depressed and febrile, with accompanying signs of shock and toxemia. A prompt and accurate diagnosis followed by aggressive medical and/or surgical intervention can often prevent an otherwise fatal outcome.

Recently, transabdominal ultrasonography has become an integral part of the diagnostic evaluation of the

the fetus and find the point at which the posterior muscles of the buttocks come together and form a definite cleavage on the ventral midline (see Figure 5.22-3, *F*). Next, the cleavage should be followed posteriorly to the tailhead. If the fetus is a female, a clitoris will appear as a small round structure in the cleavage shortly before the tailhead is reached (see Figure 5.22-2, *D*). If the small round structure is too close to the tailhead, it could be the anus. If the midline or cleavage line is followed anteriorly, the mammary gland in the female (see Figure 5.22-2, *E*) or the prepuce and penis in the male are encountered (see Figure 5.22-2, *H*, and 5.22-3, *D*). A mammary gland appears as a triangular, slightly denser tissue than surrounding muscle tissue. Each half of the gland may have two bright hyperechoic teats and slightly dense areas; a translucent division between halves of the mammary gland may also be present (see Figures 5.22-1, *C*, and 5.22-2, *E*). If the prepuce is viewed from a cross-section across the posterior ventral abdomen, it will appear as a cone-shaped structure off the ventral abdominal wall just posterior to the urachus (see Figure 5.22-3, *D* and *E*). The prepuce may appear as a cone shaped structure with a hyperechoic area within the cone. The hyperechoic area is the penis itself (see Figure 5.22-3, *E*). Sometimes the shaft of the penis can be seen with a hyperechoic distal segment (see Figure 5.22-2, *H*).

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or cecum, large colon impaction or torsion, or vascular compromise of a segment of bowel as a result of mesenteric rents or trauma. Several of these conditions can cause the affected mare to rapidly become depressed and febrile, with accompanying signs of shock and toxemia. A prompt and accurate diagnosis followed by aggressive medical and/or surgical intervention can often prevent an otherwise fatal outcome.

Recently, transabdominal ultrasonography has become an integral part of the diagnostic evaluation of the

equine abdomen. The quantity and cellularity of fluid accumulated in the ventral abdomen is readily seen with a 3.5-MHz probe. However, detection of abnormalities in peritoneal fluid is still extremely useful when managing equine colic. The significance of these abnormalities in peripartum mares that are experiencing abdominal discomfort has only recently been widely appreciated. Intuitively, because peritoneal fluid composition reflects the pathophysiologic state of the visceral and parietal mesothelial surfaces, one would anticipate that the mechanics of the foaling process (and certainly obstetrical manipulations) would be likely to incite some changes in peritoneal fluid composition.

### OBTAINING A PERITONEAL FLUID SAMPLE IN A PERIPARTURIENT MARE

The mare is sedated with xylazine hydrochloride (0.3 mg/kg of body weight, IV) and butorphanol tartrate (0.01 mg/kg, IV) if needed. The most dependent portion of the ventral abdomen is clipped, shaved, and aseptically prepared. The abdominocentesis is performed as far cranial as possible, and approximately half an inch to the right of midline, to avoid penetrating the spleen or gravid uterus. An 18-gauge, 1.5-inch needle is introduced through the skin and slowly advanced into the abdominal cavity. If no fluid is obtained, the needle should be repositioned. Sometimes rotation of the needle or injection of a small volume of air with a sterile syringe is necessary to facilitate drainage of fluid. A minimum of 1.0 ml of peritoneal fluid should be collected in a tube that contains sodium ethylenediaminetetraacetic acid (EDTA) as an anticoagulant. In clinically ill mares, it may be difficult to obtain a sample, especially if the mare is dehydrated or has a large ventral plaque of edema that extends cranially from the mammary glands. If difficulty is experienced in obtaining a sample, a local anesthetic block can be made over the site and a stab incision made through the skin, subcutaneous tissue, and muscular fascia with use of a number 15-scalpel blade. A blunt teat cannula or sterile female catheter can then be carefully advanced into the peritoneal cavity. The incision is allowed to heal by second intention.

Potential risks of an 18-gauge needle used to perform abdominocentesis include inadvertent laceration of the spleen or intestinal puncture (enterocentesis). Contamination of the sample with blood is more likely to be caused by penetration of superficial blood vessels or vessels in the abdominal musculature. This does not affect the usefulness of the sample because as much as 17% blood contamination does not alter the interpretation of the nucleated cell count or the total protein concentration of peritoneal fluid samples. Inadvertent enterocentesis may cause a transient increase in the nucleated cell count. Studies have shown that intestinal puncture with a needle rarely causes clinical signs of disease. Likewise, repeated abdominocentesis at 24- to 48-hour intervals has been shown to not alter the peritoneal fluid composition. Thus monitoring progressive changes in the peritoneal fluid may alert the clinician to the presence of a deteriorating condition in the abdominal cavity.

### PERITONEAL FLUID ANALYSIS

The peritoneal fluid is visually inspected for color and clarity (turbidity). Specific gravity and total protein concentration (TPr) estimations can be made with a hand-held refractometer. Total white blood cell (WBC) counts can be determined manually with a hemocytometer, or measured by using an automated analysis system. Differential white blood cell counts can be made by viewing 100 cells on a smear that is stained with Wright's stain. A direct smear can be made if the WBC count exceeds 10,000 cells/ $\mu$ l. When the count is low the sample should be centrifuged to concentrate the cells. The white blood cell population of the peritoneal fluid consists of a mixture of nondegenerate neutrophils and large mononuclear cells. The latter are a combination of mesothelial cells that desquamate from the peritoneal surface, as well as blood-borne monocytes and macrophages that have migrated into the peritoneal cavity.

Normal values for an adult horse may vary between laboratories. A sample is classified as a transudate if the total protein concentration is less than 2.5 g/dl and the nucleated cell count is less than 5000 cells/ $\mu$ l. Modified transudates are characterized by an increase in TPr concentration or WBC count. If the total protein concentration exceeds 3.0 g/dl and the nucleated cell count exceeds 10,000 cells/ $\mu$ l then the sample is classified as an exudate. The normal differential WBC count is approximately 60% neutrophils and 40% mononuclear cells. As much as 70% neutrophils (%N) is considered normal in equine peritoneal fluid. In acute inflammatory processes (i.e., peritonitis) the %N in peritoneal fluid may increase to 85% to 100%.

Assessment of cell morphology through cytologic examination is an extremely important part of any peritoneal fluid analysis. The morphologic characteristics of the cell types can be used to differentiate between septic and nonseptic inflammation. Nondegenerate neutrophils predominate in transudates and mild exudates. Degenerate neutrophils are characterized by nuclear pyknosis, karyorrhexis, karyolysis, and cytoplasmic vacuolization. A large number of degenerate neutrophils indicates bacterial toxin-induced cell disruption, and they predominate in septic effusions, and a guarded-to-grave prognosis is warranted. Detection of phagocytosed bacteria confirms the presence of a septic process.

### EFFECT OF OBSTETRIC CONDITIONS ON PERITONEAL FLUID

#### Uterine Torsion

In this author's experience presurgical peritoneal fluid samples from uncomplicated uterine torsion cases have not revealed any values outside of the normal range. If neglected or misdiagnosed, mares may develop significant uterine compromise that results in changes in the composition of the peritoneal fluid. WBC counts in excess of 10,000 cells/ $\mu$ l in conjunction with total protein levels above 3.0 g/dl are cause for concern. When abnormalities are detected, the expense of a ventral midline celiotomy to evaluate the condition of the uterus may be justified. Alternatively, results of peritoneal fluid analysis may support a decision for euthanasia on economic grounds.

## Normal Foaling Process

In prepartum animals and in mares with uncomplicated deliveries (oxytocin-induced or natural foaling), peritoneal fluid is clear to yellow unless it is red-tinged as a result of blood contamination. The WBC count in the postpartum samples may be increased compared with the prefoaling values, but should remain within the normal range for the laboratory. This slightly increased peritoneal fluid mononuclear cell count (WBC still  $<5000$  cells/ $\mu$ l) seen in foaling mares may be caused by normal hemodynamic changes in the immediate postpartum period. When the fetus is delivered, pressure on the great vessels is removed and the volume of peritoneal fluid may decrease. Thus, the cellularity of the remaining fluid would be expected to increase. Although the WBC count in clinically normal postdystocia cases also remains at less than 5000 cells/ $\mu$ l, the increased cellularity is the result of an influx of neutrophils, probably in response to hyperemia and increased endothelial permeability. However, any bruising and inflammation within the uterine wall is generally not severe enough to cause leakage of protein-rich fluid. The TPr should remain at less than 2.5 g/dl.

## Obstetric Cases

It may be beneficial to obtain a peritoneal fluid sample from referred obstetric cases. In most instances the foal will be dead, and the fluid analysis will provide a baseline that can document preexisting conditions (e.g., uterine tear) before further vaginal intervention. Evidence of a laceration would warrant an immediate cesarean section. The duration of the dystocia before successful fetal extraction does not appear to affect the composition of the peritoneal fluid. In difficult obstetric cases that have been subjected to prolonged manipulations before referral to a veterinary hospital, the peritoneal fluid profile is generally not altered from the normal range. The author has managed cases with an emphysematous or macerated fetus in which the composition of the peritoneal fluid samples was not abnormal. Dystocia itself does not necessarily cause significant changes in the peritoneal fluid. If an experienced obstetrician performs the vaginal manipulations and/or fetotomy the fluid should remain grossly normal.

The author has studied the peritoneal fluid from more than 50 cases that remained clinically normal after resolution of a dystocia. None of the median values changed significantly in the peritoneal fluid of these postdystocia mares. However, although the median WBC counts remained within the laboratory reference limit ( $<5000$  cells/ $\mu$ l), some mares did develop slightly increased cell counts. Although TPr exceeded normal limits (as high as 3.4 g/dl) in 3 cases, the cell count never exceeded 10,000 cells/ $\mu$ l in mares that remained clinically normal. The preponderance of neutrophils may reach 90% in some cases. Only one mare had more than one peritoneal value elevated on either day 1 or day 2. In this author's experience, those mares that are destined to become clinically ill will have at least two of the TPr, WBC count, and percent neutrophil values significantly elevated above the normal reference range.

As might be expected, mares that experience postdys-

tocia complications have significantly higher median peritoneal fluid values for TPr, WBC count, and percent neutrophils than do mares that make an uneventful recovery. The markedly increased WBC counts in the mares with uterine tears or with vaginal lacerations involving the peritoneal cavity will cause the peritoneal fluid to appear cloudy, with a dark orange color from the increased erythrocyte numbers. These cases are likely to have TPr, WBC count, and percent neutrophil values that exceed 3.0 g/dl, 15,000 cells/ $\mu$ l, and 80%, respectively. WBC counts often exceed 50,000 to 100,000 cells/ $\mu$ l. A mare with a partial thickness uterine tear is unlikely to have elevated TPr or WBC counts immediately postpartum. However, the peritoneal fluid values may be increased within 2 to 3 days depending on the severity of the damage to the uterine wall.

The normal parturient process in the mare does not entail epithelial loss from the endometrium. An intact endometrium appears to be able to prevent absorption of endotoxin and bacteria, whereas devitalization permits diapedesis and peritoneal contamination. Peritonitis is likely to develop subsequent to severe necrotizing endometritis as areas of transmural necrosis extend through the myometrium to the uterine serosa. Complete perforation of the uterine wall is not necessary for peritonitis to develop if traumatic obstetric manipulations have damaged the uterine wall. However, recent research has proven that even a fetotomy procedure does not alter the composition of the postpartum peritoneal fluid if it is performed correctly.

Cases with rupture of the uterine artery and associated development of a broad ligament hematoma tend to have markedly elevated TPr values (as high as 5.0 g/dl), but the WBC count is likely to remain within the normal range ( $<5000$  cells/ $\mu$ l). Broad ligament inflammation around a uterine artery hematoma may explain the high protein levels seen in these cases. Specific gravity values are inevitably increased if the TPr is elevated. A tear in the broad ligament subsequent to a uterine artery rupture invariably results in a bloody tap, with an elevated red blood cell count in the peritoneal fluid. Even if a clot has contained most of the hemorrhage within the broad ligament, there is often considerable blood loss into the peritoneal cavity. In this author's opinion these mares should not be transported, because movement could destabilize the clot and prove fatal. Postpartum hemorrhage is discussed in detail in Chapter 5.34.

Rupture of the mesocolon is unlikely to cause an immediate increase in the WBC count. However, the compromised segment of bowel soon loses its integrity and a massively increased WBC count (as high as 150,000 cells/ $\mu$ l) can occur within 48 hours as peritonitis ensues. An intussusception of the uterine horn can cause an elevated TPr (3.0 g/dl), but the WBC count tends to remain low unless necrosis has developed in more chronic cases. Retroperitoneal abscessation can be a life-threatening complication following a dystocia. Affected mares exhibit signs of toxemia, and the peritoneal fluid is likely to develop an increased TPr content (3.0-5.0 g/dl) and a massive increase in the WBC count (often exceeding 100,000 cells/ $\mu$ l). These retroperitoneal abscesses often develop from infected hematomas. Thus, retroperitoneal hema-

tomas in a postpartum mare warrant prophylactic broad-spectrum antibiotic coverage.

Repeated abdominocentesis is indicated in cases where clinical signs suggest that a parturient related abdominal lesion may be present, because the peritoneal fluid constituents may change within hours. Several studies have shown that repeated abdominocentesis is not detrimental to the horse and does not cause significant changes in the peritoneal fluid composition. If indicated, a series of peritoneal fluid analyses may provide useful information about the progression and seriousness of the condition. A single, elevated peritoneal fluid value (either TPr, WBC, or percent neutrophils) is likely to be an incidental finding, whereas two or more elevated values may signal the onset of clinical abnormalities. This author's clinical experience has been that if a postpartum peritoneal fluid sample has TPr greater than 3.0 g/dl in conjunction with WBC count

greater than 15,000 cells/ $\mu$ l and a WBC differential count of greater than 80% neutrophils (especially if degenerative changes are present) then a potentially life-threatening lesion is likely. However, peritoneal fluid values should not be viewed in isolation. An abnormal peritoneal fluid analysis must be considered in conjunction with the history and clinical signs that are exhibited by the mare.

### Supplemental Readings

- Frazer G, Burba D, Paccamonti D et al: The effects of parturition and peripartum complications on the peritoneal fluid composition of mares. *Theriogenology* 1997; 48:919-931.
- Van Hoogmoed L, Snyder J, Christopher M et al: Peritoneal fluid analysis in peripartum mares. *J Am Vet Med Assoc* 1996; 209(7):1280-1282.

## CHAPTER 5.24

# Placentitis

MATS H.T. TROEDSSON  
Gainesville, Florida

The equine placenta consists of the allantochorion, the allantoamnion, and the umbilical cord. The chorionic portion of the allantochorion is attached to the endometrium by microcotyledons that are present throughout the uterus, with the exception of a small area at the internal os of the cervix called the *cervical star*. The allantochorion supports the fetus *in utero*. This structure provides respiratory and nutrient exchange between the mare and the fetus and is an endocrine organ for maintenance and normal development of the fetus. The "free floating" allantoamnion allows the fetus to move freely within the uterus. The only attachment between the fetus and the allantoamnion is at the umbilicus. The umbilicus contains two umbilical arteries, one umbilical vein, and the urachus. The length of the cord and the length of the allantoic and amniotic portions can vary, but is normally 50 to 100 cm long.

Pregnancy loss during late gestation can be the result of fetal illness, placental dysfunction, maternal illness, or a combination of these factors. A functional placenta is necessary for a normal development of the fetus. Any insult or disruption of normal anatomy or physiology of the placenta may result in placental insufficiency and abortion. Compromised placental anatomy or function is the most common cause of abortions in late gestational mares. Placental insufficiency may be noninfectious (e.g., twin pregnancy) or infectious. Effective management of twin pregnancies has reduced this cause of abortion, and

placentitis has become one of the most common cause of abortion in late gestational mares.

### ETIOLOGY

The most common route of infection is believed to be ascension through the cervix. An ascending infection may be the result of a failure of the external genital barriers to protect the uterus from bacterial or fungal invasion (e.g., defective perineal conformation, nonfunctional vestibulovaginal fold, or cervical lacerations). The possibility of bacterial contamination entering the uterus at the time of breeding or the presence of a preexisting low-grade endometritis with clinical signs that develop several months later has not been critically investigated. The characteristic location of the lesions away from the cervix in mares with placentitis caused by a *Nocardioform actinomycete* raises the question of whether the microorganism may enter the uterus before, or at the time of breeding, without causing a clinical problem until later during the pregnancy. Hematogenously spread placentitis occurs but is considered to be less common than an ascending route of infection.

The most commonly isolated microorganisms from mares with placentitis are *Streptococcus zooepidemicus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Nocardioform actinomycete*, *Aspergillus* spp., and *Candida* organisms. The mechanism of abortion as a result of placentitis is not



tomas in a postpartum mare warrant prophylactic broad-spectrum antibiotic coverage.

Repeated abdominocentesis is indicated in cases where clinical signs suggest that a parturient related abdominal lesion may be present, because the peritoneal fluid constituents may change within hours. Several studies have shown that repeated abdominocentesis is not detrimental to the horse and does not cause significant changes in the peritoneal fluid composition. If indicated, a series of peritoneal fluid analyses may provide useful information about the progression and seriousness of the condition. A single, elevated peritoneal fluid value (either TPr, WBC, or percent neutrophils) is likely to be an incidental finding, whereas two or more elevated values may signal the onset of clinical abnormalities. This author's clinical experience has been that if a postpartum peritoneal fluid sample has TPr greater than 3.0 g/dl in conjunction with WBC count

greater than 15,000 cells/ $\mu$ l and a WBC differential count of greater than 80% neutrophils (especially if degenerative changes are present) then a potentially life-threatening lesion is likely. However, peritoneal fluid values should not be viewed in isolation. An abnormal peritoneal fluid analysis must be considered in conjunction with the history and clinical signs that are exhibited by the mare.

### Supplemental Readings

- Frazer G, Burba D, Paccamonti D et al: The effects of parturition and peripartum complications on the peritoneal fluid composition of mares. *Theriogenology* 1997; 48:919-931.
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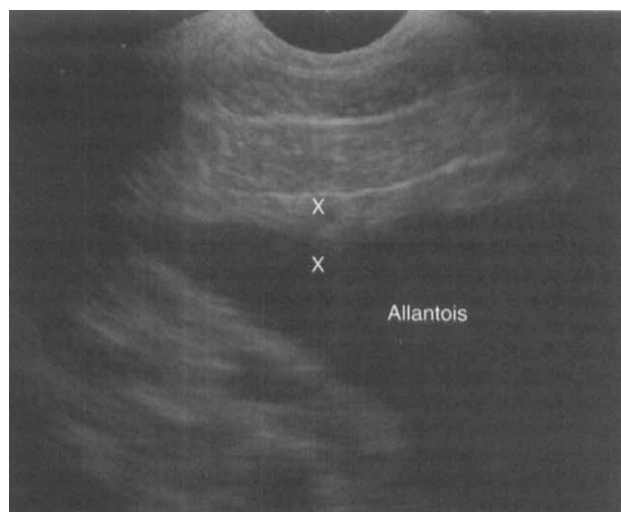
**Figure 5.24-1** Placentitis and abortion of a 10-month-old fetus. Note the chorionic area adjacent to the cervix (cervical star [a]); the thickened, discolored area of the chorion, which is depleted of villi (b); and normal chorion (c).

fully understood, but it most likely involves infection of the fetus, hormonal changes, the release of inflammatory mediators, and deprivation of the fetus of nutrients.

### CLINICAL SIGNS AND DIAGNOSIS

Clinical signs include those observed in mares with pending abortion. Udder development, premature lactation, and cervical softening are often seen before the mare aborts. Vaginal discharge may or may not proceed abortions. Once clinical signs develop, the disease has reached an advanced stage and treatment may not always be successful.

Evaluation of the equine placenta should routinely be performed after abortion or parturition. In aborting mares with an ascending placentitis, the pathologic lesions are characteristic. An area of the chorion adjacent to the cervical star is depleted of chorionic villi and is thickened, discolored, and covered by fibronectrotic exudate (Figure 5.24-1). Placentitis caused by *N. actinomyces* causes characteristic lesions at the ventral aspect of the base of the gravid horn and nongravid horn at the junction between the body and the horn of the placenta. The chorionic surface is thickened and covered with brown-red, thick, mud-like material. Placentitis caused by a hematogenous route of infection shows less characteristic multifocal lesions of the chorionic surface of the placenta. A thorough inspection of the placenta is necessary to ensure that any existing lesions are found. Examination of the placenta postpartum provides excellent information on disease processes or dysfunctions that could have affected the well being of an aborted fetus, or that may potentially cause illness in the neonatal foal. However, this examination does not aid the clinician in decisions that are aimed to prevent abortion or neonatal diseases of the foal. Evaluation of the placenta in the pregnant mare must be performed by the use of ultrasonography and endocrine tests.



**Figure 5.24-2** Transabdominal ultrasonographic image of the placenta of a late-gestational mare. Note combined thickness of the uterus and the placenta (CTUP) is labeled (x—x). (Modified from Troedsson MHT, Sage AM: Fetal/Placental Evaluation in the Mare, Ithaca, NY, International Veterinary Information Services, 2001.)

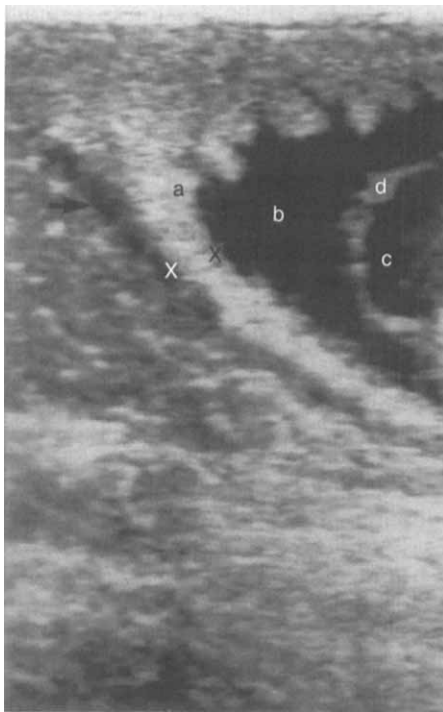
### Ultrasonographic Evaluation of the Equine Placenta

#### Transabdominal Ultrasonography

Ultrasonographic examinations of the placenta in mares that are considered to be at risk for abortion during late gestation can be performed by a transabdominal approach (Figure 5.24-2). With a 5- or 7.5-MHz sector scanner, four quadrants of the placenta should be examined; right cranial, right caudal, left cranial, and left caudal. With this technique, mares with normal pregnancies should have a minimal combined thickness of the uterus and the placenta (CTUP) of  $7.1 \pm 1.6$  mm, and a maximal CTUP of  $11.5 \pm 2.4$  mm. Pregnancies with an increased CTUP have been associated with the delivery of abnormal foals. The caudal portion of the allantochorion cannot be imaged with transabdominal ultrasonography, which prevents the clinician from diagnosing ascending placentitis in its early stages. However, placental thickening and partial separation of the allantochorion from the endometrium may be observed with transabdominal ultrasonography in mares that have placentitis originating from a hematogenous infection. In addition, a pocket of hyperechoic fluid can be seen at the base of the lowest area of the gravid uterus in mares with placentitis caused by *N. actinomyces*. Mares that graze on endophyte-infected fescue often experience retained placenta, premature separation of the allantochorion, and increased allantochorion weight and thickness. A significant increase in uteroplacental thickness and premature separation of the allantochorion has been found on transabdominal ultrasonographic examination of endophyte-infected mares. However, the thickness was not observed until an average of 8 hours before the onset of labor.

#### Transrectal Ultrasonography

Transrectal ultrasonography of the caudal allantochorion in late gestational mares provides an excellent image of the



**Figure 5.24-3** Transrectal ultrasonographic image of a late-gestational mare. Note the placenta adjacent to the cervix (a); the allantoic fluid (b); the amniotic fluid (c); the amniotic membrane (d); the middle branch of the uterine artery (arrow); and the combined thickness of the uterus and the placenta (x—x). (Modified from Renaudin C, Troedsson MHT, Gillis C et al: Ultrasonographic evaluation of the equine placenta by transrectal and transabdominal approach in pregnant mares. *Theriogenology* 1997; 47:559-573.)

placenta close to the cervical star (Figure 5.24-3). A 5-MHz linear transducer should be positioned 1 to 2 inches cranial of the cervical-placental junction, and then moved laterally until the middle branch of the uterine artery is visible at the ventral aspect of the uterine body. The CTUP should then be measured between the middle branch of the uterine artery and the allantoic fluid (Figure 5.24-4; see Figure 5.24-3). The clinician has to make sure that the amniotic membrane is not adjacent to the allantochorion, because this may result in a falsely increased CTUP. The CTUP should be measured in the ventral part of the uterine body. The CTUP in the dorsal part of the uterus is often thicker than in the ventral part of the uterus. In addition, placental parts of the dorsal uterus have often been found to be edematous in normal pregnant mares during the last month of gestation (see Figure 5.24-3). Normal values for CTUP are illustrated in Table 5.24-1. An abnormal thickness and partial separation of the allantochorion from the endometrium has been observed on ultrasonographic examination in mares with clinical signs of ascending placentitis (Figure 5.24-5). A CTUP greater than 8 mm between day 271 and 300, less than 10 mm between day 301 and 330, and greater than 12 mm after day 330 has been associated with placental failure and pending abortion. In advanced stages, the space between the uterus and the placenta is filled with hyperechoic fluid.



**Figure 5.24-4** Transrectal ultrasonographic image of a late-gestational mare. Note the middle branch of the uterine artery (a); the combined thickness of the uterus and the placenta (CTUP; x—x); and normal edema of a dorsal portion of the placenta (arrow). (Modified from Troedsson MHT, Sage AM: Fetal/Placental Evaluation in the Mare, Ithaca, NY, International Veterinary Information Services, 2001.)

**Table 5.24-1**

**Normal Upper Limits for the Combined Thickness of the Uterus and the Placenta during Late Gestation**

Gestational Period	CTUP
151-270 days	<5 mm
271-300 days	<7 mm
301-330 days	<9 mm
331 +	<12 mm

Modified from Renaudin C, Troedsson MHT, Gillis C et al: Ultrasonographic evaluation of the equine placenta by transrectal and transabdominal approach in pregnant mares. *Theriogenology* 1997; 47:559-573.

Although transrectal and transabdominal ultrasonographic examination of the placenta is useful to detect early signs of some placental pathology, the clinician should keep in mind that placental changes resulting in periparturient problems can be subtle and not readily detected on ultrasonographic examination.

## Endocrine Monitoring of the Placenta

### Progesterone

The equine placenta is part of an endocrine fetal-placental interaction that synthesizes and metabolizes progestogens. This endocrine function of the placenta is important for maintenance of pregnancy after the endometrial cups and the secondary corpora lutea disappear at ap-



**Figure 5.24-5** Transrectal ultrasonography of an abnormal placenta in a mare during the ninth month of gestation. The external border of the uterus is outlined by black spots. The combined thickness of the uterus and placenta (CTUP; + ---- +) is abnormal (11 mm) at this stage of gestation, and the placenta is separated close to the cervix (arrow). (Modified from Troedsson MHT, Sage AM: Fetal/Placental Evaluation in the Mare, Ithaca, NY, International Veterinary Information Services, 2001.)

proximately day 150 of gestation. Mares with advanced stages of placentitis or placental separation may have increased plasma concentrations of progestogens as a result of stress to the fetal-placental unit. In contrast, circulating progestogens have been reported to fall below normal after fetal hypoxia and infection with equine herpesvirus. Although increased concentrations of plasma progesterone during mid and late gestation would suggest placentitis, therapeutic decisions should not be made on the basis of one sample. Serial blood samples need to be obtained from an individual mare in order to detect a clinically useful trend in progesterone concentrations. Fetal-placental progesterone is rapidly metabolized to 5-pregnanes, and the metabolites may not be recognized by commercial progesterone assays. Therefore maternal serum progesterone concentrations in late pregnant mares do not accurately reflect the conditions in the uterus. Monthly blood sampling of mares at risk of abortion showed no differences in plasma progesterone concentrations in mares with impending abortion and mares with normal pregnancies.

### Estrogen

Both estradiol and conjugated estrogen (estrone sulfate) are elevated during late pregnancy in mares. Estrone sulfate in maternal serum is thought to be a marker of fetal well-being. However estrogens have not been useful to detect early signs of placentitis.

### Relaxin

Relaxin is produced by the equine placenta and can be detected in peripheral blood plasma from day 80 of gestation and throughout the pregnancy. The role of relaxin during pregnancy is not fully understood, but some evidence ex-

ists that placental relaxin production is compromised in mares at risk of aborting their fetuses. No commercial test for equine relaxin is currently available, and more research needs to be performed to evaluate the usefulness of plasma relaxin as a clinical tool to diagnose placentitis and to monitor the efficacy of treatment strategies.

## TREATMENT AND PREVENTION

Treatment of mares with placentitis should focus on elimination of the infectious agents, reduction of the inflammatory response, and reduction of the increased myometrial contractility in response to the ongoing inflammation. No controlled studies have been reported on the efficacy of treatments for mares with placentitis, and the following recommendations are based on clinical experience and extrapolation from other species.

Urine pooling, cervical lesions, and poor perineal conformation should be corrected to prevent an ascending route of infection during pregnancy. Mares with abnormal placental findings on ultrasonographic examination or clinical signs of placentitis should be treated with broad-spectrum antibiotics, antiinflammatories (flunixin meglumine, 1.1 mg/kg q12h; or phenylbutazone, 4 mg/kg q12h), and tocolytics (altrenogest, 0.088 mg/kg q24h; or clenbuterol, 0.8 µg/kg q12h). Pentoxifylline (7.5 mg/kg PO q12h) is thought to increase oxygenation of the placenta through an increased deformability of red blood cells. A bacterial culture should be obtained in mares with vaginal discharge for isolation of a causative agent and sensitivity to antibiotics. After foaling or abortion, the uterus of the mare should be cultured and the mare should be treated for endometritis if the culture is positive.

Mares have been reported to deliver normally developed foals several weeks or even months after successful treatment of placentitis. No current diagnostic method exists, however, to predict how the compromised uterine environment in a mare with placentitis will affect the development of her fetus in individual cases.

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## CHAPTER 5.25

## Placental Hydrops

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**H**ydrops is a rare condition in the mare, with hydroallantois occurring more commonly than hydroamnios. Hydroallantois causes rapid abdominal enlargement during the last trimester of pregnancy (Figure 5.25-1), and a sudden increase in the volume of allantoic fluid during a period of 10 to 14 days. The pathophysiology of hydroallantois in the mare remains unknown. Some authors have suggested that the increase in fluid is a placental problem caused either by increased production of fluid or decreased transplacental absorption. Others have proposed that the etiology is related to placentitis and heritability. In these authors' experience, examination of the fetus and fetal membranes have rarely demonstrated any consistent abnormality. One mare had diffuse mild placentitis (with leptospirosis) and another had histologic evidence of vasculitis when an endometrial biopsy was taken within 2 days of delivery of the fetus.

Mares may present with anorexia, tachycardia, severe ventral edema/plaques, abdominal discomfort, and labored breathing caused by pressure on the diaphragm. They typically have difficulty walking and often become recumbent. Uterine rupture may occur in advanced cases. Other complications associated with the excessive weight of the uterine contents include prepubic tendon rupture and development of abdominal wall and inguinal hernias.

Rectal palpation is diagnostic and reveals a huge, taut, fluid-filled uterus. The fetus cannot be balloted. Transrectal ultrasound imaging shows hyperechogenic allantoic fluid. The fetus is seldom observed as a result of the depth of the enlarged uterus. Transabdominal ultrasound will confirm the presence of excessive echogenic allantoic fluid and this approach does permit evaluation of fetal viability (movement and a heart rate of 80-100 bpm).

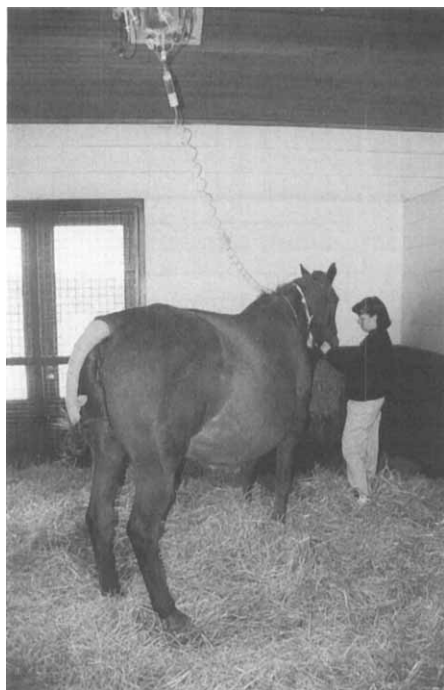
### TREATMENT

During the last few years the medical facility at these authors' clinic has seen an increase in the number of hydroallantois cases presented to the clinic. Once the diagnosis of hydroallantois is confirmed, fetal viability is determined, and udder development and the milk electrolytes are assessed to estimate the level of fetal maturity. Those mares that present early in gestation may undergo elective termination of pregnancy by IM injection of cloprostenol (500 µg, 2 ml IM q12h until delivery).

Cases that occur later in gestation, or those with profound abdominal enlargement, may have large volumes of fluid within the uterus and require controlled drainage of the fluid before expulsion of the fetus. The reason for the controlled drainage is that excessive uterine distention alters total body fluid balance and venous return to the right heart. Sudden loss of this large volume of fluid may result in hypovolemic shock. The effect of the fluid loss is exacerbated by the sudden expansion of the abdominal venous circulation once the uterine weight is reduced. In the short term, abdominal support (i.e., belly band), IV fluids, steroids, broad-spectrum antibiotics, and antiinflammatory medication will provide systemic support for the mare. Slow siphoning of the allantoic fluid is then attempted. Once the size of the distended uterus has been reduced, the authors have used oxytocin (20 IU IV given repeatedly or 50 IU in a saline drip) or cloprostenol (two doses of 500 µg, 30 minutes apart) to promote fetal expulsion. In these authors' experience, cloprostenol has provided a smooth progression of labor, with stage 2 occurring 30 to 60 minutes after the second dose. Mares that present within the last 2 to 4 weeks of pregnancy may be managed by partial drainage. The aim in these cases is to maintain the pregnancy for as long as possible in order for additional fetal maturation to occur.

The technique for drainage involves several considerations. Location (stocks or stall) is determined by individual preference and the condition of the mare. The process takes 2 to 3 hours, so comfort is a factor. The clinician should initiate supportive care by placing an IV catheter and administering a slow infusion of a crystalloid fluid. A tail wrap and sterile surgical preparation of the mare's perineum is essential. The equipment includes a 24- to 32-French sharp thoracic trocar catheter, a two-way plastic adapter, sterile plastic tubing, a sterile sleeve, and buckets to collect the allantoic fluid. Smaller-sized catheters will take longer for fluid removal. The technique involves sterile passage of the catheter through the vagina and cervix, and sharp puncture of the chorioallantois. The sharp trocar is removed and the two-way adapter is used to connect the catheter to the tubing. The catheter is held in place by the clinician's arm within the vagina. Controlled gradual drainage can then be performed into the buckets. Some pericervical separation of the placenta is common.

Several mares have been successfully treated in these authors' hospital with this technique. In a few cases (6)



**Figure 5.25-1** Excessive abdominal distention in a mare with placental hydroallantois.

that were within 2 to 4 weeks of term, maintenance of the pregnancy has been attempted after partial drainage of the allantoic compartment. These mares were treated with additional antimicrobial therapy, antiinflammatory medications (flunixin meglumine, pentoxifylline), agents with possible tocolytic activity (isoxsuprine, clenbuterol, albuterol), and altrenogest. In cases where partial drainage is attempted, fetal death may occur as a result of fetal asphyxia that results from varying degrees of placental separation. Iatrogenic fetal infection, secondary to contamination of the placental fluids during drainage, is also a

problem. In most cases attempted to date, the fetus has become infected with *Escherichia coli* and subsequently died. One mare died after 72 hours as a result of rupture of a uterine artery. The fetus in that mare had remained alive and exhibited normal parameters when monitored by transabdominal ultrasound.

Owners should be advised that the fetus is usually lost in mares with hydroallantois. However, early recognition of the problem, and prompt intervention, provides a good prognosis for the mare both physically and reproductively. Complications that should be anticipated when managing a mare with hydroallantois include hypovolemic shock, dystocia, and retention of the fetal membranes. The hypovolemia requires rapid volume expansion with use of large volume crystalloid infusion (as high as 40 ml/kg) alone, or in combination with hypertonic saline (4 ml/kg). The use of colloid fluids such as hetastarch (10 ml/kg) might also be beneficial. Dystocia may be associated with incomplete cervical dilation and uterine inertia. Malpositioning and malpostures are common. Therefore manual assistance to deliver the foal is necessary. Management of retained fetal membranes is discussed elsewhere in this text (see Chapter 5.35: "Retained Fetal Membranes"). Because it is possible that a heritable component to this condition exists, breeding to a different stallion may be prudent.

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## CHAPTER 5.26

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# Clinical Problems in the Breeding Stallion

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### PENILE AND PREPUTIAL TRAUMA

Balanitis is inflammation of the free body, or the glans penis, and posthitis is inflammation of the laminae of the prepuce. Balanoposthitis is inflammation of both areas. Phimosis is the inability of the stallion to completely protrude its penis from the prepuce. This condition usually results from constriction of the external preputial orifice or the preputial ring, either subsequent to trauma or as a result of neoplasia. Urine scalding can exacerbate the problem because of excoriation and cellulitis. Paraphimosis is prolapse of the penis and inability to retract it into the preputial cavity.

Kicks received during natural breeding are a common cause of penile and preputial injury. Severe penile trauma may result from bending of the erect shaft as a result of sudden movement of the mare during intromission. Unlike penile hematomas in the bull, the hemorrhage in stallions is often not from the blood spaces of the corpus cavernosum penis. Blunt trauma to the penile shaft can result in inflammatory edema and hemorrhage from the venous plexus external to the tunica albuginea of the penis (Figure 5.26-1). However, if the hematoma continues to expand, then surgical exploration may be warranted to repair a possible tear in the tunica albuginea itself. Ultrasonographic examination is useful to evaluate the extent of the tissue damage. Because the mare's tail hairs can cut the penis, the mare's tail should always be wrapped before breeding. Lacerations can also be caused by Caslick's and breeding stitches, or by improperly fitted, cracked, or wrinkled phantom covers. The erect penis of a stallion also can be traumatized by attempts to breed an estrous mare across a fence.

The severe inflammatory response associated with penile trauma leads to prolapse of the detumescing penis as well as the internal preputial lamina. Venous and lymphatic drainage are greatly impaired by the acute swelling and pendulous weight, and the condition becomes self-perpetuating. If the condition is chronic, the veins may have thrombosed and the lymphatics may be clogged or occluded by the swelling. The stretched penile and preputial epithelium rapidly becomes dry and cracked, leading to excoriation and infection. Neglected cases can result in the development of extensive cellulitis. Superficial lacerations of the penis and prepuce should be treated aggressively to prevent complications.

### Treatment

When presented with a stallion with penile and preputial trauma, the clinician must determine whether the animal can urinate. The volume of urine in the bladder can be determined by palpation per rectum. If necessary the bladder should be catheterized. Urethral patency must then be monitored until the penile and preputial swelling subsides. If the injury is acute, application of ice packs wrapped in wet towels may help to prevent edema if the stallion will tolerate these manipulations. Cold-water hydrotherapy should be continued until threat of further edema or hemorrhage has passed. The clinician should not overdo hydrotherapy because it can lead to skin maceration. Skin creams and wound ointments are useful to protect the traumatized epithelium. Gentle massage will help to reduce edema. The clinician can apply a rubber pressure bandage for short periods, starting at the glans penis and wrapping upwards. The injured penis should be replaced into the preputial cavity as soon as possible.

If an irreducible paraphimosis is present then the edematous penis and prepuce should be elevated and supported to facilitate venous and lymphatic drainage of the injured tissue. Some sort of external support for the penis and prepuce (e.g., nylon mesh attached to four pieces of cotton gauze) must be constructed. Failure to support this pendulous weight will exacerbate the edema and can cause damage to nerve fibers that may ultimately lead to penile paralysis. After ensuring that the stallion can void urine, the clinician's next priority is to support the injured organ against the ventral abdomen. Loose nylon mesh is ideal because it permits urine drainage and does not trap moisture. Pantyhose can be easily fashioned into a sling (Figure 5.26-2). Nonsteroidal antiinflammatory medication and regular exercise (with penile support) may help reduce inflammatory edema. This author has found warm water hydrotherapy to be useful in stimulating fluid resorption. The penis and preputial epithelium must be well covered with ointment to prevent any macerating effect of the hydrotherapy. Prompt and diligent care of an acute injury may relieve the inflammatory edema within 3 to 4 days. Once the edema is reduced, the penis and internal laminae of the prepuce should be returned to the preputial cavity, and retained by a supporting truss or temporary retention sutures. The disadvantage of sutures is that they will further traumatize the friable preputial

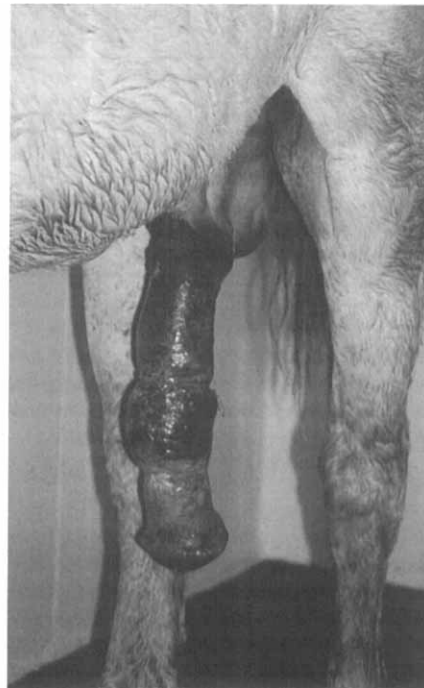


**Figure 5.26-1** Paraphimosis in a stallion. The penile epithelium had become dried and cracked, which has caused secondary cellulitis. Note the significant scrotal swelling that can negatively affect semen quality.



**Figure 5.26-2** Support of the injured penis is essential for adequate venous and lymphatic drainage. Hosiery can be readily fashioned into a sling. In some cases the stallion may need to be fitted with a bib to prevent self-inflicted trauma.

tissue. The horse should receive broad-spectrum antibiotic coverage to prevent cellulitis. The stallion should be isolated from mares to enforce sexual rest until the tissues have completely healed. If significant scrotal edema has been associated with the condition the owner should be advised that the stallion's semen quality may be adversely affected for a couple of months. When the stallion is returned to the breeding shed, the semen should be monitored for evidence of hemospermia.



**Figure 5.26-3** Persistent penile erection (priapism) in a stallion. Medical therapy is often ineffective, and irrigation of the corpus cavernosum penis with heparinized saline may be warranted.

## PENILE PARALYSIS

Although flaccid paraphimosis (penile paralysis) may be a complication of severe penile injuries, the condition may also be associated with some neurologic diseases (e.g., rabies, equine herpesvirus [EHV]-1 myelitis, or spinal injuries); the edema of purpura hemorrhagica, equine viral arteritis, and equine infectious anemia; severe debilitation; and administration of certain phenothiazine-derived tranquilizers such as propipromazine and acepromazine maleate. The flaccid paraphimosis may or may not be edematous. Given time, the skin of the exposed glans and free body of the penis becomes dried, thickened, and inelastic. If the condition is chronic, the prognosis is bleak for a breeding stallion. Some horses with penile paralysis may be trained to ejaculate into an artificial vagina if the water temperature in the vagina is increased. The stallion can be salvaged for nonbreeding purposes by surgically retracting the penis (phallopexy; also known as the *Bolz technique*) or by amputation (phallectomy).

## PRIAPISM

Priapism or persistent penile erection is uncommon in stallions but has been associated with the administration of phenothiazine-derivative tranquilizers. A drug-induced blockade of sympathetic impulses to smooth muscles associated with the erectile process may permit the corpus cavernosum penis to fill with blood such that the penis drops from sheath (Figure 5.26-3). If the condition is acute, administration of a cholinergic blocker (bentropine mesylate, 8 mg IV) may be an effective treatment.



Although antiinflammatory medication, massage, and supportive slings are unlikely to resolve the condition, they do help to reduce the amount of secondary edema that can develop. Emollient ointments are useful to protect the exposed tissues. As time progresses the stagnant blood in the corpus cavernosum penis eventually occludes the venous outflow and then the arterial inflow.

An aggressive approach provides the best prognosis. When priapism is diagnosed the corpus cavernosum penis should be flushed with heparinized saline to remove the sludged blood. A large-gauge needle is inserted into the cavernous tissue behind the glans penis. A second large gauge needle is then inserted into the corpus cavernosum penis approximately 4 to 6 inches behind the scrotum. The irrigation is continued until all dark sludged blood has been evacuated. In recurrent cases, a surgical procedure has been described to create a shunt from the corpus cavernosum penis to the corpus spongiosum penis. If treatment is unsuccessful then phallectomy may be required.

## PENILE NEOPLASMS AND GRANULOMAS

The grouping of neoplasms with granulomas is appropriate because they have features in common both in differential diagnosis and surgical management. Both groups are space-occupying lesions that are frequently ulcerated and associated with local hemorrhage, exudation and regional irritation. A final diagnosis should depend on biopsy results, and not on clinical impressions. Biopsy results are essential for establishing a rational basis for treatment.

### Squamous Cell Carcinoma

Squamous cell carcinoma is the most common neoplasm of the equine penis and prepuce. Breeds that tend to have unpigmented genitalia (e.g., Appaloosa, American Paint Horse) are most commonly affected. Usual sites are the glans penis, the skin of the free body of the penis, and the preputial ring. Initially small, heavily keratinized plaques appear. The lesion infiltrates the underlying tissue and creates a shallow, crusted, fungoid, and ulcerative neoplasm. Lesions tend to remain localized and although the squamous cell carcinoma is malignant, the progress is very slow. However, ultimately penile invasion and metastasis to the superficial inguinal lymph nodes occurs if the condition is neglected. Rapidly growing secondary tumors in the area of the inguinal lymph nodes may have necrotic centers and sinuses that drain a purulent discharge. In these advanced cases the penis may be trapped within the preputial cavity as inflammatory edema and fibrosis prevent the prepuce from performing its normal telescoping function.

#### Treatment

Precancerous lesions (carcinoma *in situ*) may be treated by applications of 5-fluorouracil. Small penile and preputial neoplasms are amenable to cryosurgery or 5-fluorouracil. Surgical excision of pedunculated, nonmetastatic lesions and segmental posthioplasty (reefing) may salvage erectile function. The goal of surgical intervention is to remove

the lesion and fibrotic tissue while maintaining or restoring the telescoping action of the prepuce. The stallion will require as much as 4 weeks of sexual rest before teasing to gauge success of the procedure. The amount of prepuce that the clinician can surgically remove without affecting normal coital function is difficult to predict. In advanced cases in which the neoplasm has invaded the tunica albuginea, a phallectomy (penile amputation) and removal of lymph nodes is necessary. The stallion should be castrated a couple of weeks before the amputation is performed. If the tumor has invaded the penis, prepuce, and lymph nodes, then radical dissection with complete ablation and perineal urethrostomy may be necessary to salvage the animal. However, economic and humane factors must be considered.

## Cutaneous Habronemiasis

"Summer sores" are caused by infestation of the skin and mucous membrane with *Habronema* sp. larvae. The house and stable fly are the nematode's intermediate hosts, and are prevalent during the summer months. Predilection sites are the urethral process and the preputial ring. Lesions on the preputial ring may cause interference with the normal telescopic action of the prepuce, and may lead to a phimosis. Lesions on the urethral process tend to cause hemospermia once the corpus cavernosum penis has been exposed. Migration and encystment of the larvae cause the development of exuberant granulation tissue. Histologic evaluation of a biopsy specimen will reveal an intense eosinophilic reaction with caseous granules and encysted larvae.

#### Treatment

Antiinflammatory medication may help to alleviate the foreign body reaction against the larvae. The widespread use of ivermectin and related anthelmintics has reduced the incidence of this condition. The larvicidal activity of systemic ivermectin will kill most larvae after a single treatment. This leads to rapid clinical improvement, and resolution of the lesions within a month in most instances. Topical organophosphate application (4.5 gm trichlorfon in 2-oz. nitrofurazone cream mixed with an antiinflammatory agent, applied once daily) can be effective. Systemic treatment with organophosphate is not without risk, and the stallion has to be monitored for signs of toxicity. The clinician must have atropine and pralidoxime chloride available.

Focal residual scar tissue in the internal lamina of the prepuce can be surgically removed under local anesthesia. Larger lesions warrant a reefing procedure. If amputation of the urethral process is required, the cut edges must be carefully closed with several fine interrupted sutures. A postoperative complication can be hemospermia associated with tearing of residual scar tissue at the suture site during the penile engorgement that is associated with ejaculation.

## EQUINE COITAL EXANTHEMA

EHV-3 is distinct from the rhinopneumonitis viruses. It causes an infectious venereal disease with an incubation

period of 6 to 10 days. At that time small, raised, red-denied, vesicular blisters (2-5 mm diameter) appear. These develop into pustular papules with an increased number of lesions appearing during a 2- to 5-day period. By the sixth day, most of initial pustules have become encrusted, scab-like lesions. The scabs are easily rubbed off to reveal superficial ulcers. The penis and prepuce may be painful and edematous resulting in temporary unwillingness of the stallion to penetrate the mare or artificial vagina. In fact, to prevent transmission, the stallion should be withheld from stud service until the genital lesions are healed. Failure to rest the stallion can delay healing and will promote the spread of infection to susceptible mares. Similar lesions occur on the vulvar mucosa of affected mares. The condition is self-limiting. In the interim the penis and prepuce should be cleansed, and emollient ointments applied. Fertility does not decrease in uncomplicated cases. If no secondary infection exists, the lesions resolve within 2 to 3 weeks, leaving depigmented white scars.

## HEMOSPERMIA

The presence of blood in the ejaculate (hemospermia) may be detrimental to fertility. Blood in the ejaculate may be associated with urethritis, habronemiasis of the urethral process, and lacerations of the glans penis, but is often caused by tears in the urethra. The etiology of these urethral defects is unknown, but the likely source of the hemorrhage is the corpus spongiosum penis. The site of the lesion is typically at the level of the ischial arch on the posterior surface of the urethra. Confirmation of the diagnosis requires examination of the urethra with a long, sterilized, flexible endoscope.

Some cases of hemospermia have been treated medically with methenamine and antimicrobial drugs. Although recommendations for sexual abstinence are justified, this approach alone is often unsuccessful in correcting the problem. A temporary urethrostomy at the level of the ischial arch may be more effective. This procedure may reduce the pressure in the corpus spongiosum penis during the muscular contractions associated with micturition. If the urethral defect can be seen, then sutures stitched into the tear may be beneficial.

## EFFUSIONS OF THE VAGINAL CAVITY

### Hematocele

An acute hematocele is a collection of whole blood from hemorrhage in the vaginal cavity. In some cases the scrotal sac may be so distended that it is quite firm on palpation. Hematoceles are almost invariably associated with trauma to the scrotal contents. A hematocyst is a hematoma that is confined within the tunica albuginea. Typically the stallion will exhibit signs of pain, especially in response to attempts to palpate the distended scrotum. Ultrasonographic examination will reveal the presence of free-floating echogenic spots that swirl as the scrotum is balloted. In less-acute cases the blood will have clotted and the image will consist of echogenic clots and free-floating fibrin tags, interrupted by anechoic serous fluid. If the tunica albuginea of the testis has been ruptured then the distorted tes-

ticular architecture may be detected by ultrasonographic examination. Needle aspiration with aseptic technique will reveal serosanguineous fluid.

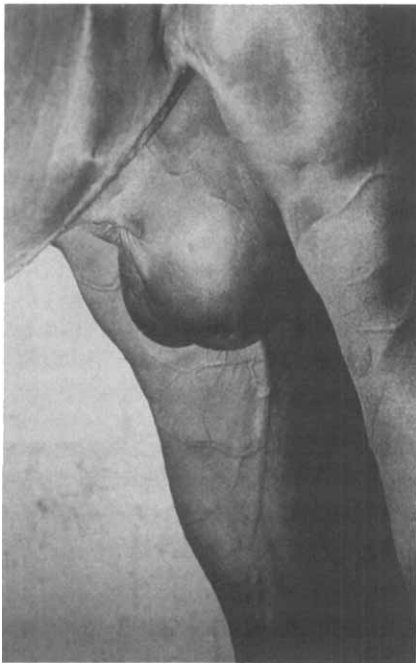
A small hematocele may resolve without treatment, but adhesions between the visceral and parietal tunics may preclude normal thermoregulation. A breeding soundness examination should be performed 60 days after resolution. If the testis is not freely mobile within the vaginal cavity then semen quality may be adversely affected. If a large hematocele is present, then the blood will insulate the testis and adversely affect spermatogenesis. Surgical intervention may be warranted to drain the cavity and identify the source of the hemorrhage. A small rent in the tunica albuginea may be amenable to suturing, but concerns about the negative effects of inflammation on the contralateral testis often justify unilateral orchiectomy. Gross damage to the testis and/or epididymis leave the surgeon little alternative.

### Hydrocele

A hydrocele is a painless, noninflammatory accumulation of serous fluid between the visceral and parietal layers of the vaginal tunic. Although scrotal enlargement resulting from excess fluid accumulation may be associated with other pathology (e.g., neoplasia), in many instances the condition is idiopathic. The etiology is presumed to be associated either with increased secretion of fluid by the vaginal tunic, or decreased resorption by the veins and lymphatics of the spermatic cord. The condition may be of acute onset, or it may develop insidiously.

Because the condition is not painful, the immediate concern is primarily for the stallion's subsequent fertility. The testicular temperature will be elevated as a result of the insulating effects of fluid accumulation. This will have a detrimental effect on spermatogenesis in the affected testicle, and may adversely impact on the contralateral testis as well. Some cases are transient, and appear to be associated with hot weather. They may self-correct with the onset of cooler environmental temperatures. If the condition is chronic then the affected testis is likely to atrophy.

The inguinal rings should be examined per rectum to check for the presence of an inguinal or scrotal hernia, although in most instances the stallion would be expected to exhibit signs of colic associated with strangulation of an intestinal loop. Palpation of the scrotal contents may be unrewarding, depending on the amount of scrotal distention (Figure 5.26-4). A mild shifting fluctuance, or an edematous scrotal sac that is grossly distended with fluid, may be present. In these instances ultrasonographic examination is especially useful. The fluid accumulation in a hydrocele produces an anechoic to hypoechoic ultrasound image. If the ultrasound examination confirms that the fluid is in the sac of the tunica vaginalis, then a needle aspirate may be obtained using aseptic technique. The stallion should be monitored systemically for fever, pain, and leukocytosis. Because the vaginal sac is an extension of the peritoneal cavity, fluid accumulation can occur as an extension of peritonitis or ascites. This author managed a case of diffuse peritonitis with an elevated white cell count in the vaginal cavity fluid. Clinicians should use caution when aspirating fluid from a hydrocele because the needle



**Figure 5.26-4** Distention of the vaginal sac can be caused by an accumulation of serous fluid (hydrocele) or blood (hematocele). An ultrasonographic examination is useful in confirming the diagnosis.

can lacerate a vessel on the tunica albuginea and cause significant hemorrhage. Aspiration of serous, amber colored fluid from the vaginal cavity verifies the presence of a hydrocele. Therapeutic drainage is not a viable option because the fluid soon reforms.

#### **Treatment**

Treatment options for a hydrocele are limited. Because the etiology of the fluid accumulation is poorly understood it is difficult to propose viable solutions. If the condition is secondary to scrotal trauma, then antiinflammatory medication and cold water hydrotherapy may help to reduce the acute edema. Exercise may also help in the short-term, and occasionally a hydrocele will spontaneously resolve. However, because most hydroceles are persistent, the usual course of action to manage the condition is unilateral castration to remove the affected vaginal tunic and testis. Failure to do so may lead to adverse temperature related effects on spermatogenic function in the contralateral testis as well.

### **INGUINAL AND SCROTAL HERNIAS**

An inguinal hernia is the passage of a segment of intestine through the vaginal ring into the inguinal canal. The hernial contents usually consist of the ileum or distal jejunum and are contained within the cavity of the tunica vaginalis. In the canal they share the vaginal sac with the testicular vessels and ductus deferens. A scrotal hernia occurs when the intestines descend into the scrotum and lie adjacent to the testis (Figure 5.26-5). The condition is generally considered to be acquired when diagnosed in an adult stallion. However, the predisposing cause may have been a congenitally enlarged vaginal ring. Although the



**Figure 5.26-5** Scrotal hernia in a stallion usually causes severe colic. This condition is a surgical emergency and often requires a ventral midline celiotomy to resect a strangulated loop of intestine.

condition may be reported to occur after breeding, exercise, or transport, it can also occur in a stallion that has been resting in a stall.

Affected stallions have an awkward gait and generally develop severe colic symptoms because the segment of intestine almost invariably becomes compromised. The scrotum may or may not be swollen, depending on whether an inguinal or scrotal hernia is present, and the duration of the condition. Even inguinal hernias can result in scrotal and testicular edema because the intestinal loop compresses the spermatic cord. Acute pain from a testicular torsion must be considered as one of the differential diagnoses. Palpation of inguinal rings per rectum is important if a stallion presents with colic signs. Omentum and/or intestine may be palpated entering the ring. If the hernia has self-corrected, the affected ring is still likely to feel enlarged. If the scrotum is enlarged there may be palpable crepitus, and an ultrasonographic examination may confirm the presence of loops of intestine.

#### **Treatment**

Emergency ventral midline celiotomy is necessary to resect the incarcerated loop of small intestine because acute, irreducible hernias commonly become strangulated. Attempts to save the affected testicle may be impractical because vascular compromise may have already occurred. Also, many surgeons prefer to remove the involved testicle so that the inguinal ring can be completely closed. If the unaffected testis is not removed, some compensatory hypertrophy may occur. Because a propensity to develop hernias may be inherited, it may be ethical to recommend castration at the time of surgery.

## LESIONS OF THE TESTICLES

### Hypoplasia and Atrophy

Testicular hypoplasia is a congenital condition involving failure of the testis to develop normally. The affected testis is small and of soft consistency. The condition may be associated with a chromosomal abnormality. In degenerative atrophy, loss of spermatogenic tissue occurs in what had been a normally developed testis. The affected testis becomes small and firm. It is often difficult to determine a precise cause (e.g., disturbance of thermoregulation) and the clinician has to rely on historic information. Both conditions result in decreased sperm production. Even if only one testicle is atrophic, sperm production may still be insufficient to classify the stallion as breeding sound.

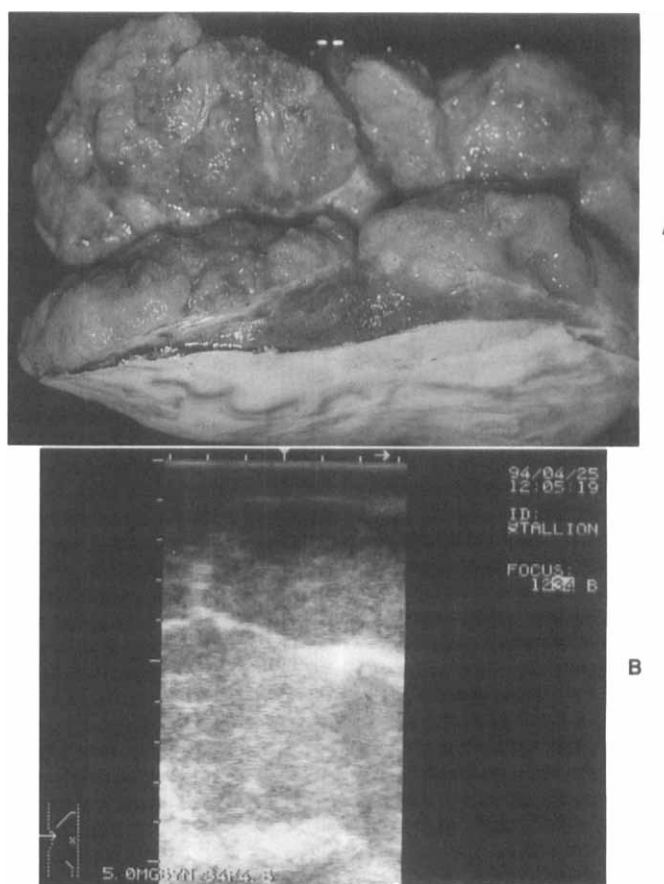
### Orchitis

Orchitis is generally associated with sterile inflammation, and often is of traumatic origin. Infectious orchitis is uncommon, but may be the result of ascending infection (e.g., infection with *Klebsiella* organisms) or to localization of systemic disease (e.g., streptococcal infection). Penetrating wounds are more common and will cause swelling and abscessation. The testicle is often hot, painful, and very tense as a result of swelling that is confined by the tunica albuginea. Fluctuant swelling is not a reliable diagnostic feature. A superimposed edematous plaque in the scrotal skin generally makes palpation difficult. The stallion is likely to be febrile. Systemic antimicrobials, antiinflammatory medication and hydrotherapy may help, but prompt unilateral orchiectomy often is indicated to minimize thermal damage to the contralateral testis.

### Neoplasia

Testicular neoplasia in stallions is uncommon. Neoplasia presents as a nonpainful testicular enlargement of insidious onset. The affected testicle usually remains freely movable within the scrotum. Testicular lymphatic drainage flows into the medial iliac and lumbar lymph nodes, and this can lead to metastases in the posterior abdomen and pelvis. The superficial inguinal lymph nodes would only be affected if the scrotum, penis, and prepuce were involved (see section in this chapter on squamous cell carcinoma). Ultrasonography will reveal changes in the normal homogenous echogenicity of testicular parenchyma (Figure 5.26-6, B). The image of the contralateral testis is useful for comparison. Testicular neoplasia can be confirmed by cytologic examination of a fine-needle aspirate or by histologic examination of a biopsy specimen.

A seminoma is the most common testicular tumor of aged stallions. Although they are generally benign, the clinician should suspect metastases if the spermatic cord is palpably thickened. The tumor has a gray, lobulated cut surface (Figure 5.26-6, A). Teratomas are uncommon tumors of young horses, and are most likely to be found in a cryptorchid testicle. Interstitial (Leydig's) cell tumors are rare, and have characteristic firm, tan-brown nodules on the cut surface. Sertoli's cell tumors are extremely rare testicular tumors that are firm, with a gray-white cut surface. Unilateral orchiectomy is indicated. The spermatic cord



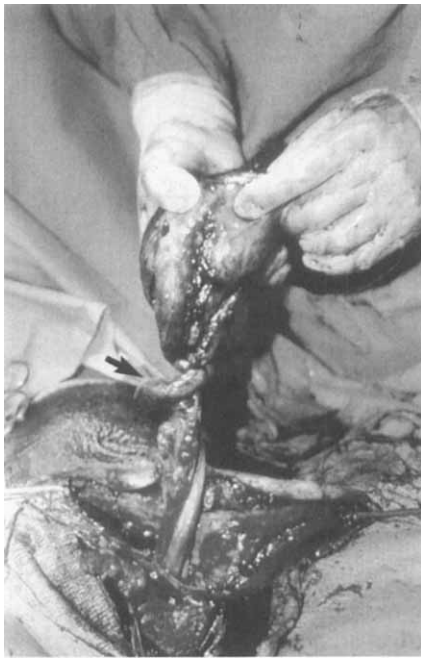
**Figure 5.26-6** **A**, The characteristic gray, lobulated cut surface of a seminoma—the most common neoplasm of the equine testis. **B**, Ultrasonographic image of a testicular neoplasm in a stallion. Note the lobulations that are suggestive of a seminoma. The image of the contralateral testis is useful for comparative purposes.

should be ligated and severed as far proximal as possible. Histologic examination of sections of the proximal cord or evidence of metastases is required before the stallion's owner is offered a prognosis.

### Torsion of the Spermatic Cord (Testicular Torsion)

Testicular torsion may occur as two different syndromes. The condition occurs when the distal spermatic cord and testicle rotate on the vertical axis. A partial torsion can be described as a rotation of 180 degrees or less. In cases of 180-degrees torsion, the tail of the epididymis is located in the cranial aspect of the scrotum. The ligament of the tail of the epididymis (gubernaculum) can be palpated as a small knob of tissue dorsal to the epididymis. These partial torsions are often an incidental finding during a breeding soundness examination. Although they should be noted in the examination report, no adverse effect on semen quality has been noted.

Torsion of more than 180 degrees starts to cause some venous and then arterial compromise of the spermatic vessels. Torsions of 360 degrees or greater cause complete oc-



**Figure 5.26-7** Surgical removal of a testis strangulated by a 360-degree torsion of the spermatic cord. The torsion had caused complete occlusion of the arterial supply to the affected testis (*arrow*).

clusion of the testicular blood supply. The affected stallion shows signs of severe colic. Ischemic damage and gangrene rapidly ensue (Figure 5.26-7). The vascular compromise leads to the slow development of scrotal swelling. In cases that have been misdiagnosed as a gastrointestinal colic, the stallion may respond to analgesic medication, and only later will the correct diagnosis be made when scrotal swelling is noticed. Thus although the condition is rare, torsion of the spermatic cord should always be considered when a stallion exhibits signs of colic. The differential diagnosis should include a strangulated loop of intestine in an inguinal or scrotal hernia. If a 360-degree torsion is present, the tail of the epididymis is in its normal position. However, the vascular compromise makes the affected cord and testicle enlarged and firm. Ultrasonographic examination of the congested cord reveals obvious differences from the unaffected side. An accumulation of fluid may be present in the vaginal sac, and hypoechoic areas may be present within the strangulated testicle.

Unilateral castration is indicated in most cases. If the condition is diagnosed immediately then an orchiopexy procedure has been described to permanently fix the testicle in its correct scrotal alignment. However, the vascular compromise is likely to have already caused some irreversible testicular damage. Ultrasonographic measurements are useful to monitor for evidence of subsequent testicular atrophy.

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## CHAPTER 5.27

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# Ventral Abdominal Hernia and Prepubic Tendon Rupture

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**R**upture of the ventral body wall can occur in all breeds during late gestation. Draft breeds appear to be at greatest risk because of their size. Older mares that lack muscle tone, mares carrying twins, hydroallantois cases, mares with severe ventral edema, or those sustaining ventral trauma, are at greater risk for abdominal herniation. These same predisposing factors can cause complete transverse rupture of the rectus abdominis muscles, or partial/complete rupture of the prepubic tendon in mares during the later part of pregnancy. The similarity in clinical presentation makes it difficult to distinguish between these conditions.

### ABDOMINAL WALL HERNIAS

The weight of the pregnant uterus on the caudal epigastric and caudal superficial veins may restrict drainage of the area, and a severe plaque of ventral edema can extend from the udder to the xiphoid. Mares with a ventral hernia present with a similar plaque of inflammatory edema. Damage to the musculature by external trauma can also cause edema. Progressive enlargement of a rent in the abdominal wall causes pain that makes affected mares walk slowly; often they are reluctant to move at all. Discomfort is displayed when the caudal abdomen is palpated. The defect and/or hernial contents are usually difficult to palpate transabdominally due to the edema. Transrectal palpation of the defect is seldom possible because of the presence of the fetus and the large, dependent uterus. Transabdominal ultrasound permits visualization of any abdominal contents that may be herniated through the rent in the body wall. Tears may be difficult to distinguish from separation of the musculature by severe edema, and careful ultrasonographic evaluation is indicated.

### Treatment

Initial treatment of a suspected hernia should be directed toward stabilization of the mare through confinement to a small area and restricting exercise. External abdominal support in the form of a belly-band should be used to transfer abdominal weight to the vertebral column. Administration of laxatives and reduction of the bulk of the ration will prevent constipation. If the foal is viable and mature, parturition should be induced to decrease the risk of uterine blood vessel rupture or enlargement of the defect to the point where abdominal discomfort and weak-

ness leads to recumbency. Induction of parturition with the use of cloprostenol (two doses of 250-500 µg, 30 minutes apart), or oxytocin (20 IU, repeated as needed, or 50 IU in a saline drip) has been effective in this author's experience. Delivery must be assisted because the mare will be unable to mount an adequate abdominal press. Excessive exertion should be minimized to prevent any enlargement of the hernia. A cesarean section should be considered if the prognosis for the mare is poor, and the viability of the foal is of primary concern. Surgery is also indicated if incarceration of a piece of bowel is suspected. If the pregnancy is not sufficiently advanced to permit delivery of a viable foal then abdominal support and supportive care should be maintained until induction or surgery is feasible.

Transverse, oblique, and ventral hernias may not be well delineated prepartum but when the edema resolves after delivery the rents will become more evident. An abdominal support should be worn for 2 to 3 months until the edema resolves and a fibrous ring forms at the sight of the hernia. Surgical repair with propylene or plastic mesh has been successfully performed. Smaller defects may heal by second intention. Reproductive capacity postrepair is not known; however, constant supervision and assistance during parturition is necessary so that further damage does not occur. In cases where defects are unable to be repaired, future pregnancies are unwise. Embryo transfer or other new assisted reproduction technologies may be the best option. These procedures are discussed in Chapters 5.16 through 5.21.

### RUPTURE OF THE PREPUBIC TENDON

The tunica flava abdominis with the transverse abdominal, internal abdominal oblique, and rectus abdominis muscles forms the ventral support of the abdomen. The prepubic tendon serves as the tendon of insertion for the lamina externa of the rectus abdominis, gracilis, and pectineus muscles. The tendon attaches to the cranial border of the pubis including the iliopubic eminence. Although the causes and presentation of prepubic tendon rupture are similar to those of abdominal hernias, a differentiation can be made because mares with a prepubic tendon rupture are reluctant to lie down and display a characteristic stance. Affected mares have a lordosis and an elevation of the tuber ischii and tail head (Figure 5.27-1). Tension on the mammary gland can produce a hem-



**Figure 5.27-1** Mare with ruptured prepubic tendon. Note the pendulous abdomen, lordosis, and elevation of the tuber ischii and tail head.

orrhagic secretion resulting from ruptured blood vessels. Death can occur from prepubic tendon rupture.

Diagnosis is difficult, especially with partial tears. The condition must be differentiated from abdominal wall hernias, edema of late pregnancy, hydroallantois, hydramnios, and nonreproductive conditions such as right-sided heart failure, vasculitis, and neoplasia. In this author's experience this condition frequently occurs as a complication of hydroallantois. Rectal palpation of the ventral abdominal wall is not always possible. Transabdominal ultrasound will support the diagnosis.

Because surgical repair is not possible, supportive care and abdominal support should be provided for the mare until the foal can be delivered. If the foal is viable and ma-

ture, induction of parturition should be initiated. Unfortunately, problems usually arise because of the lack of abdominal press and the gravity-dependent foal in the heavy uterus—thereby making delivery difficult and obstetric assistance imperative. When the foal is dead, malpositioning and malpostures should be expected. In most cases the prognosis of the mare is poor, or death is imminent. In the latter case, humane destruction (shooting) with removal of the foal transabdominally or by cesarean section may provide the foal the best chance for survival. In this author's experience the survival of both the mare and the foal is rare. If the mare does survive, rebreeding is not recommended. Embryo transfer and other new assisted reproductive techniques may permit salvage of superior genetics.

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## CHAPTER 5.28

# Uterine Torsion

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The causes of uterine torsion in the mare are not well-defined. The condition is much more common in cattle; in that species a large, term fetus has been implicated as a major risk factor. The majority of uterine torsions in cows occur at term and most are thought to be a direct result of fetal positional changes during late first-stage and early second-stage labor. A striking difference between the mare and the cow is that more than 50% of uterine torsions in mares occur before the end of gestation. In this author's clinical experience the vast majority occur before term, and other authors have reported on

cases from as early as 8 months of gestation. Owners who work closely with their mares may mention that they have observed excessive fetal movements in the flank area. In a recent equine obstetrical study, 80% of term fetuses were found to be in dorsosacral position when the uterine torsion was corrected. This finding suggests that fetal righting reflexes may have played a role in creating the torsion. This author believes that vigorous fetal movements during the latter stages of gestation are likely to be a significant factor in the etiology of this condition in the mare (Figure 5.28-1).





**Figure 5.27-1** Mare with ruptured prepubic tendon. Note the pendulous abdomen, lordosis, and elevation of the tuber ischii and tail head.

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## CHAPTER 5.28

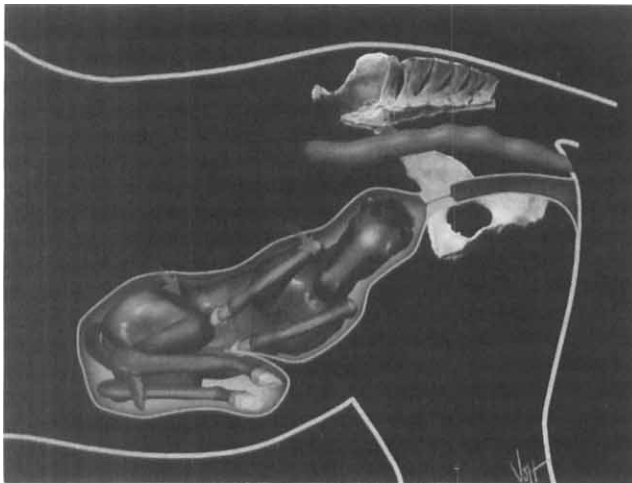
# Uterine Torsion

GRANT S. FRAZER  
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**T**he causes of uterine torsion in the mare are not well-defined. The condition is much more common in cattle; in that species a large, term fetus has been implicated as a major risk factor. The majority of uterine torsions in cows occur at term and most are thought to be a direct result of fetal positional changes during late first-stage and early second-stage labor. A striking difference between the mare and the cow is that more than 50% of uterine torsions in mares occur before the end of gestation. In this author's clinical experience the vast majority occur before term, and other authors have reported on

cases from as early as 8 months of gestation. Owners who work closely with their mares may mention that they have observed excessive fetal movements in the flank area. In a recent equine obstetrical study, 80% of term fetuses were found to be in dorsosacral position when the uterine torsion was corrected. This finding suggests that fetal righting reflexes may have played a role in creating the torsion. This author believes that vigorous fetal movements during the latter stages of gestation are likely to be a significant factor in the etiology of this condition in the mare (Figure 5.28-1).



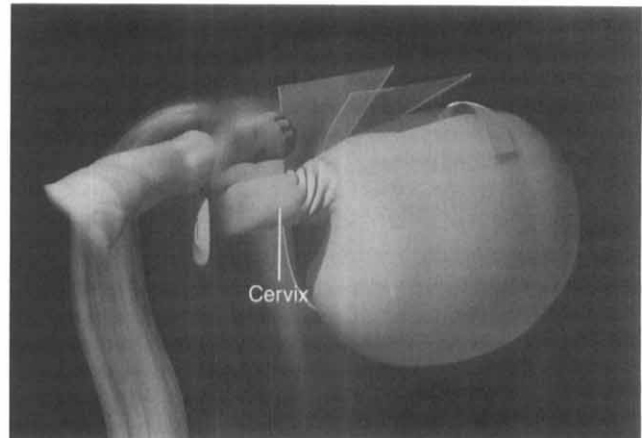


**Figure 5.28-1** The cause of uterine torsion in the mare is not known. This author believes that vigorous fetal movement during the last trimester is likely to result in rotation of the entire uterus.

## DIAGNOSIS

The clinical signs that first attract the owner's attention are the result of abdominal pain. These signs may include restlessness, sweating, anorexia, frequent urination, sawhorse stance, looking at the flanks, and kicking at the abdomen. When the veterinarian is first summoned the signs may have been present for a couple of hours, but sometimes for 3 days or more, especially if they are intermittent and moderate. In mares that are close to term the owner may assume that the signs are indicative of impending parturition. In more extreme cases the signs will be more severe, and may be associated with concurrent involvement of the small or large colon. Veterinarians should always consider the possibility of uterine torsion when presented with a mild, persistent colic in a mare that is in the last trimester of gestation. Delay in making a definitive diagnosis increases the likelihood of fetal compromise. Occasionally the condition may remain undiagnosed for 2 to 4 weeks. In these instances an owner may have attempted treatment with analgesics that they have used for previous mild colic episodes. This author has managed one case where the referring veterinarian was not contacted until the owner became concerned that the mare had not responded and was now inappetent and lethargic. Sometimes the veterinarian may incorrectly diagnose the condition as a mild gastrointestinal colic and initially treat the mare medically with analgesics and mineral oil.

Thus palpation per rectum is essential to determine the presence of a uterine torsion. This author believes that all late pregnant mares that display signs of mild to moderate colic warrant a thorough rectal examination to rule out the possibility of uterine torsion. Although vaginal involvement in the torsion is very common in the cow, uterine torsions in the mare seldom cause detectable changes in the vagina. Thus vaginal examination is generally not diagnostically useful. On palpation per rectum the clinician should aim to carefully examine both broad liga-

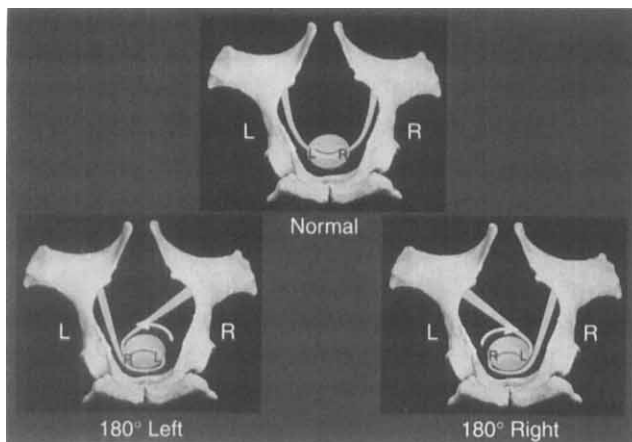


**Figure 5.28-2** When the gravid uterus rotates, the displaced broad ligament is pulled forward in front of the ligament on the side of the torsion. Thus when the clinician's arm is advanced into the rectum, the side on which the taut broad ligament is first encountered will correspond to direction of the torsion (left or right). The clinician can then confirm the direction of the torsion by palpating the ligaments (see Figure 5.28-3).

ments, starting in the dorsal lumbar region and moving in a ventral direction. An accurate examination will confirm the diagnosis, determine the direction of the torsion, and give some idea of the severity of the condition. If a uterine torsion is present the two ligaments will meet where they pass under the uterus. Location of the ovaries may aid in the identification of the ligaments. The ligament on the side of the torsion tends to be more caudal, and is palpable as a tight vertical band (Figure 5.28-2). The opposite ligament is pulled horizontally across the top of the uterus before being displaced ventrally (Figure 5.28-3). A transrectal ultrasound examination is useful to evaluate the condition of the fetal fluids and to note if any placental detachment has occurred.

The compressive forces of the displaced broad ligaments may cause variable amounts of constriction of the small colon. In one 360-degree, uterine torsion case that the author managed the constriction was such that it was not possible to perform a complete internal evaluation. In these cases determination of the direction of the torsion can be extremely difficult, if not impossible. The condition of the uterine wall in the vicinity of the torsion can be assessed by cautiously advancing a linear array transducer along the rectal floor past the area of the constriction. The degree of uterine compromise can be gauged by noting the thickened uterine wall and distended vasculature on the ultrasound image. Compression of the veins and lymphatics in the broad ligaments and at the site of the torsion occurs before occlusion of the arterial blood supply. Thus the initial changes will be associated with pooling of fluid within the uterine wall.

This author routinely uses transabdominal ultrasonographic imaging to assess fetal viability (heart rate and rhythm) and to evaluate the condition of the fetal fluid. Abdominocentesis can provide prognostic information



**Figure 5.28-3** Careful palpation of the broad ligaments per rectum can confirm the direction and severity of a uterine torsion. The ligament from the opposite side will be pulled horizontally across the top of the uterus, and the ligament on the side of the torsion will be pulled tightly down under the uterus.

and guide the clinician in choosing a mode of correction. Uterine rupture is an uncommon complication of uterine torsion in the mare. In this author's experience mild uterine torsions, or those of short duration, do not alter the color, cellularity, or total protein content of the peritoneal fluid. Any alterations in the composition of the peritoneal fluid may indicate the presence of a compromised or ruptured uterine wall. This information will facilitate the choice of the correct surgical approach or support a decision for euthanasia if economic considerations preclude surgical intervention. A flank laparoscopic examination can confirm the condition of the uterine wall.

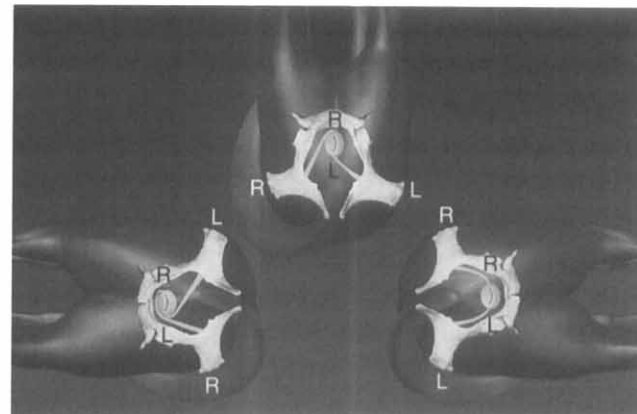
## CORRECTION

### Torsion in the Term Mare

If the mare is at term and the cervix is sufficiently dilated to permit passage of a well-lubricated arm into the uterine body, then it may be possible to grasp the fetus ventrolaterally. The fetus and uterus must be rocked back and forth until sufficient momentum is achieved to continue up in an arc, and thus roll both fetus and uterus back into a normal position. More than 80% of term torsions can be corrected in this manner. Another option is to attach an obstetrical chain to a fetal limb, loop through the eye of a detorsion rod, then place this loop around the other limb. Extreme caution must be exercised so as not to injure the fetus or cause damage to the mare's reproductive tract. If used judiciously this technique may facilitate safe rotation of the fetus and uterus.

### Rolling the Mare

More typically the mare is preterm and an alternate approach must be used. Although not employed by the author, one inexpensive technique involves rolling the anesthetized mare in an attempt to rotate the mare's body

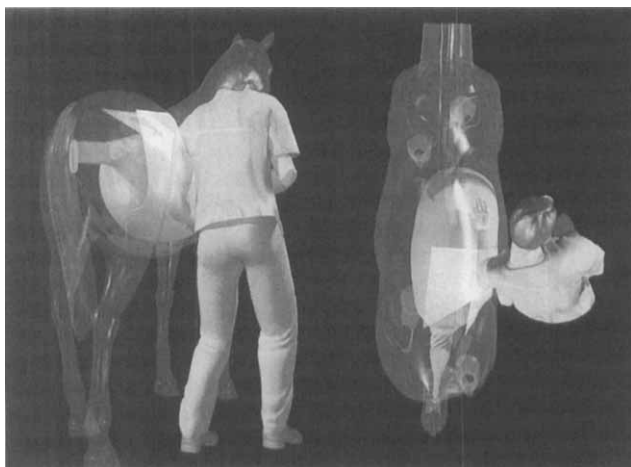


**Figure 5.28-4** If the clinician is to correct the torsion by rolling the anesthetized mare, accurate determination of the direction of the displacement is essential. In this example of a right-side torsion the mare has been placed in right lateral recumbency. Note that the position of the uterus does not change as the mare is rolled. Successful correction occurs when the left side of the pelvis comes to lie on the ground adjacent to the left side of the uterus.

around the stationary gravid uterus. Placement of the mare in lateral recumbency on the side of the torsion is essential (Figure 5.28-4). The aim of the procedure is to roll the mare such that the pelvis "catches up" with the uterus, and this method will fail if the uterus rotates with the rest of the mare's body. To prevent this, additional pressure may be applied to the fetus and uterus by ballottement of the mare's abdomen, or by placing a plank of wood against the flank and having a moderately built person stand on it. The plank must be positioned so that some portion of it is always directly over the uterus while the mare is rolled from lateral recumbency, through dorsal recumbency, and then into lateral recumbency on the opposite side. Correction by rolling the mare is controversial. Citations in the literature report on a limited number of cases. Drawbacks to this approach include the chance that unsuccessful attempts to correct the torsion will prolong its adverse effects; the fact that if the direction of the torsion is misdiagnosed, rolling the mare may make the condition worse; inability to visually assess the condition of the uterus; and the potential to create a displaced colon. In addition, a higher risk of placental detachment and uterine rupture is reported. Another concern is that if general anesthesia is induced under less than ideal conditions then fetal hypoxia may result. In cases of uterine torsion the oxygen delivery to the fetus may already be compromised by hypoperfusion of the placental unit, and anesthesia-induced maternal hypoxia could result in a critical fetal oxygen deficit. Thus although the rolling procedure may be appealing from an economic viewpoint, the owner should be informed of the potential complications.

### Surgical Correction of Uterine Torsion

A standing flank laparotomy has been the method of choice for the majority of cases on which this author has



**Figure 5.28-5** The standing flank approach for correction of a uterine torsion. An incision is made on the same side as the direction of the torsion.

worked. Intractable mares should be operated on under general anesthesia. In the standing flank approach a grid incision is made on the same side as the direction of the torsion. The clinician corrects the torsion by placing the forearm under the uterus. If necessary, the fetal hock may be gently grasped, but care should be taken so as not to traumatize the uterus (Figure 5.28-5). The fetus and uterus are then rocked back and forth to gain momentum. A combination of lifting and rotating movements generally results in easy correction of the torsion (Figure 5.28-6). The presence of a live fetus greatly facilitates the detorsion manipulations. It has been this author's experience that more difficulty may be experienced in mares that are close to term. In these cases an incision in the opposite flank may become necessary to permit a second surgeon to assist by gently pulling across the top of the uterus as it is elevated from below. Correction of the torsion is verified by abdominal palpation of the broad ligaments, or by an assistant palpating per rectum. Finally, the uterus should be palpated for signs of edema, congestion, and hematomas that could adversely affect fetal viability or postpartum uterine involution. If the fetus is dead, the mare should abort naturally once the uterine torsion has been corrected, thereby avoiding hysterotomy and any associated complications. However, the mare should be closely monitored, and obstetrical assistance must be available to correct any malposition or malposture.

A ventral midline celiotomy has been used when concern exists about significant uterine compromise, or when the presence of another problem coexisting in the abdomen is suspected. A decision is made on the basis of clinical judgment of the condition of the mare, duration and degree of abdominal pain, level of confidence in the accuracy of the diagnosis, abnormal abdominocentesis findings, and the clinician's previous experiences with similar cases. The ventral midline approach allows the clinician to quickly and definitively correct the torsion, assess the status of the uterus, and to evaluate the abdomen for any other complications. Also, if a cesarean sec-



**Figure 5.28-6** In the standing flank approach the surgeon's arm is placed under the uterus. A gentle rocking motion is used to elevate the uterus and return it to its normal position.

tion is deemed to be necessary, it can be readily performed at that time. Although the ventral midline incision is a source of concern in a foaling mare, postoperative complications have not been a problem during subsequent parturition (Rolf Embertson, Lexington, Ky., 2000 [personal communication]).

This author managed a case of 360-degree uterine torsion in a 13-year-old Quarter Horse mare (315 days' gestation) that had been neglected for several days. The owner self-treated a "mild colic" with analgesics and did not involve a veterinarian until the mare became depressed and inappetent several days later. Abnormal peritoneal fluid with the palpation findings and ultrasound images indicated the presence of a dead fetus and a severely compromised uterus. The owner declined surgery on the basis of economic considerations. However, if the owner wants to keep the mare, offering the option of a ventral midline celiotomy and ovariectomy is possible. A recent article reported on two cases of chronic uterine torsion that were successfully resolved this way. Both mares were subsequently used for riding.

## PROGNOSIS FOR THE FETUS

The prognosis for cases of equine uterine torsion depends on the degree of vascular compromise. Severity and duration of the condition will affect placental circulation and subsequent fetal viability. In this author's experience, if the fetus is alive and the uterine wall is not severely congested and edematous, then the prognosis for both the mare's survival and for the birth of a live foal at term is good. The concept of progestin supplementation after the first 100 days of gestation remains controversial. Luteolysis can occur during early pregnancy as a result of endotoxin-mediated prostaglandin  $F_{2\alpha}$  release, and progestin supplementation has been shown to be effective in maintaining pregnancies. In late gestation a viable placenta should produce adequate amounts of progestins. If the fetoplacental unit is compromised to the extent that it is incapable of producing sufficient progestins to maintain

pregnancy then it is probable that insufficient oxygen and nutrients will be available to support the rapidly growing late gestation fetus anyway. However, progestin supplementation during late gestation may still be indicated to ensure myometrial quiescence, and thus maintenance of the placental attachment. Recent studies support the premise that progestins may suppress myometrial activity by inhibition of endogenous prostaglandin  $F_{2\alpha}$  production. Although supplementation after a uterine torsion would be in the last 2 to 3 months of gestation, reports exist of mares retaining a nonviable (died at 3 to 5 months gestation) fetus while being administered progestins. Thus if progestin supplementation is administered to a mare after correction of a uterine torsion, fetal viability should be monitored at regular intervals.

### Supplemental Readings

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## CHAPTER 5.29

# Induction of Parturition

MARGO L. MACPHERSON  
*Gainesville, Florida*

**E**lective, attended foalings are advantageous to monitor mares that have experienced dystocia or premature placental separation in previous deliveries. Mares with gestational abnormalities such as rupture of the prepubic tendon or hydroallantois may require assistance during delivery. However, induction of parturition in itself can be associated with side effects such as dystocia, premature placental separation, fetal hypoxia, and dysmaturity. Thus careful case selection before induction of parturition is critical for successful delivery.

### CRITERIA FOR INDUCTION OF PARTURITION

Before labor is induced in a mare, the ability of the fetus to survive extrauterine life must be confirmed. Several physiologic processes occur within the fetus before delivery to ensure that the foal will be viable after birth. The equine fetus is unique in that final maturation occurs only 24 to 48 hours before delivery. Consequently, the equine fetus is at substantially greater risk of dysmaturity/prematurity if delivered at an inappropriate time.

Several indicators have been identified that suggest fetal and maternal "readiness for birth." Gestational length (>330 days) is often erroneously used by those considering induction of parturition in the mare. The normal gestation period in the mare is highly variable between animals and ranges from 320 to 360 (~340) days. Most mares tend to have a similar gestational length from year to year;

thus historic information can be very useful. However day length can affect gestational length so that mares foaling during short days typically have a longer gestation than mares foaling during long days. Therefore all fetuses are not necessarily mature at 330 days from the last breeding. The length of a mare's gestation should only be used in conjunction with other signs when the decision is being made to induce parturition.

Mammary development and colostrum production in the mare are presently the most reliable indicators of fetal maturity and "readiness for birth." Colostrum is paramount to the survival of the neonate both as a source of nourishment and immunoglobulins. Furthermore, concentration of mammary secretion electrolytes has been well correlated with fetal maturity in horses. Calcium concentration rises sharply in mammary secretions of most normal mares 24 to 40 hours before foaling. Additionally, sodium concentration typically is much higher than potassium until 3 to 5 days before birth, at which time the sodium to potassium ratio inverts. Changes in mammary secretion electrolytes (calcium, sodium, and potassium) have been compared with neonatal parameters that are indicative of adequate maturity at birth. A rise in mammary secretion calcium greater than 10 mmol/L and inversion of the sodium-potassium ratio are well correlated with fetal maturity in foals.

Precise measurement of mammary secretion electrolyte concentrations requires a flame spectrophotometer or a laboratory chemistry analyzer. With these systems, elevation of

pregnancy then it is probable that insufficient oxygen and nutrients will be available to support the rapidly growing late gestation fetus anyway. However, progestin supplementation during late gestation may still be indicated to ensure myometrial quiescence, and thus maintenance of the placental attachment. Recent studies support the premise that progestins may suppress myometrial activity by inhibition of endogenous prostaglandin  $F_{2\alpha}$  production. Although supplementation after a uterine torsion would be in the last 2 to 3 months of gestation, reports exist of mares retaining a nonviable (died at 3 to 5 months gestation) fetus while being administered progestins. Thus if progestin supplementation is administered to a mare after correction of a uterine torsion, fetal viability should be monitored at regular intervals.

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Precise measurement of mammary secretion electrolyte concentrations requires a flame spectrophotometer or a laboratory chemistry analyzer. With these systems, elevation of

mammary secretion calcium to greater than 40 mg/dL and potassium concentration greater than sodium (i.e., potassium >30 mEq/ml and sodium <30 mEq/ml) usually indicates fetal maturity in the normal equine pregnancy. Stall-side tests are available to measure calcium ( $\text{Ca}^{++}$ ) or calcium carbonate ( $\text{CaCO}_3$ ) concentration. Test kits that measure mammary secretion  $\text{Ca}^{++}$  typically use pads on a test strip that change from green to red (Predict-A-Foal, Animal Health Care Products, Vernon, Calif.) or titrate a diluted sample until an indicator dye changes from pink to blue (Titret, CHEMetrics, Calverton, Va.; Sofchek, Environmental Test Systems, Elkhart, Ind.). The dilution kits are somewhat more labor-intensive than the test strip kits. Of the commercially available mammary secretion test kits, the Titret test kit is the most reliable and repeatable test for predicting foaling within 24 hours. In one study, the mammary secretion  $\text{CaCO}_3$  was between 300 and 500 ppm in most mares that foaled within 12 to 18 hours of testing. Mares with mammary secretion  $\text{CaCO}_3$  less than 200 ppm had less than a 1% chance of foaling within 24 hours of testing.

As with other induction criteria, care must be taken when changes in mammary secretion electrolyte concentrations are interpreted. Changes occur most often at night, which is when the majority of mares foal. Therefore samples taken early in the day may not reflect electrolyte changes that occur in the evening or at night shortly before parturition. Mares foaling for the first time may show rapid or no change in electrolyte concentrations before foaling. "Maiden" mares often do not have significant mammary development and colostrum production until immediately before parturition. Conversely, mares with twins or placental pathology may precociously develop a mammary gland, and mammary secretion calcium levels may rise prematurely. Thus although highly reliable for predicting fetal maturity and impending parturition in the normal, multiparous mare, mammary secretion electrolytes may be less useful for maiden mares or mares with abnormal pregnancies.

The importance of cervical dilation before the induction of parturition in the mare has been a point of great controversy. Numerous studies cited in the human medical literature associate poor cervical relaxation with failed induction, prolonged labor, and a high rate of cesarean deliveries. Reports in the veterinary medical literature suggest that inductions may proceed successfully in a mare with a tightly closed, mucous-covered cervix as late as the end of first stage labor. In one study, mares with spontaneously dilated cervixes (determined by digital examination per vagina) before induction delivered their foals more quickly than those mares with a closed cervix. Foals delivered rapidly stood and nursed more quickly and had fewer signs of intrapartum asphyxia (e.g., hypercapnia, maladjustment) than foals that experienced prolonged delivery. Prostaglandin  $\text{E}_2$  ( $\text{PGE}_2$ ) has recently been used to promote cervical relaxation before induction of mares.  $\text{PGE}_2$  is routinely administered to women to dilate the cervix before induction of labor.  $\text{PGE}_2$  enhances cervical dilation and eases delivery in treated mares. Foals delivered from  $\text{PGE}_2$ -treated mares suckle more quickly than foals from control mares. Results from these two studies indicate that cervical relaxation before parturition can positively affect neonatal health.

In summary, no one criterion effectively predicts the success of an induced parturition in the mare. Adequate udder development, changes in mammary secretion electrolytes, and cervical softening are all important considerations before induction.

## METHODS OF INDUCTION

Oxytocin is generally considered to be the drug of choice for induction of parturition in the mare. Oxytocin has a rapid effect and results in delivery within 15 to 90 minutes after administration. The progress of parturition is consistent with oxytocin and few adverse effects are noted in the term foal. Various methods and doses of oxytocin induction have been described including a bolus injection of 2.5 to 120 units oxytocin, via the intramuscular (IM) or intravenous (IV) route; IM or subcutaneous (SQ) injection of 2.5 to 20 units oxytocin at 15 minute intervals; and IV administration of 60 to 120 units oxytocin in 1 L of saline delivered at a rate of 1 unit/minute. Method of delivery of oxytocin (bolus injection, repeated incremental injections or IV drip) does not appear to affect neonatal outcome in induced deliveries. Logistically, administration of oxytocin by injection allows the mare to move about freely in a stall or paddock without human intervention. When administering oxytocin through an IV drip an individual must stand at the head of the mare at all times. Alternatively, an elaborate tubing system must be constructed to prevent the mare from becoming tangled in the drip lines as she lays down to roll or push.

The dose of oxytocin is an important consideration when parturition is induced in the mare. Initial reported doses of oxytocin ranged between 75 and 120 IU. Few untoward effects on the mare or foal were reported with these high doses of oxytocin; however, one must consider the possibility of uterine hyperstimulation with higher doses. More recently, doses of 15 to 20 units oxytocin (IV, IM, or SQ) have been used. Injections are administered at 15- to 30-minute intervals until the chorioallantois ruptures. Before further injections, a vaginal examination and evaluation of the progress and position of the fetus are critical. First-stage labor is abbreviated in induced parturition, so a higher likelihood exists that the fetus will be abnormally positioned/postured. Correction of fetal limbs should be made before administering additional oxytocin, because the expulsive effects of the mare may make it difficult to perform manipulations on the fetus later on. In all cases of induced foaling, the veterinarian should remain present through the delivery of the foal.

Recently, it has been shown that doses of oxytocin as low as 2.5 IU IV are effective in inducing the term mare. In one study, mares that had 8 mmol/L  $\text{Ca}^{++}$  in mammary secretions were considered to be near foaling, and 2.5 IU oxytocin were administered. Mares that did not foal within 1 hour of oxytocin administration were judged not ready to foal, and they received a second dose of oxytocin (2.5 IU, IV), daily, until foaling occurred. Fourteen of 17 mares (14/17, 82%) foaled after the first treatment; one mare foaled after oxytocin administration on day 2, and 2 mares foaled after oxytocin on day 3. The investigators concluded that a single, low-dose injection of oxytocin (2.5 IU, IV) was effective to induce parturition in mares.

Furthermore, the researchers suggested that this induction scheme would work only in mares with a mature fetus, and that mares foaling on days subsequent to the initial treatment did not respond to oxytocin because the fetus was not fully mature. This method of induction appears to be a safer but more labor-intensive approach for a field practitioner.

## CONCLUSIONS

In summary, several factors affect the success of induced parturition in the mare. Fetal readiness for birth is paramount to survival of the foal after birth. Critical evaluation of mammary secretion electrolytes, cervical relaxation, and gestational length facilitates proper mare selection and neonatal survivability with induced parturition. Oxytocin is the current agent of choice to induce parturition in the mare. The method of oxytocin administration does not impact neonatal adaptability after induced birth. Because a low-dose oxytocin protocol is effective for inducing parturition in the mare, higher doses of oxytocin are unnecessary and may be inappropriate.

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# CHAPTER 5.30

## Stallion Behavior Problems

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This chapter briefly outlines several of the most common behavior problems of breeding stallions. These problems include self-mutilation, inadequate libido, rowdy breeding behavior, specific erection dysfunction, mounting and thrusting difficulties, frenzied hyperactive behavior, and specific ejaculation dysfunction. Also briefly outlined is the common problem of residual stallionlike behavior in geldings.

## INADEQUATE LIBIDO

Specific stallion libido problems include slow starting novices, slow or sour experienced stallions, and specific aversions or preferences. Although certain genetic lines tend to be shy or quiet breeders, the majority of inadequate libido in stallions is man-made in the sense that it is the result of domestic rearing, training, or breeding conditions. Stallions that have been disciplined for showing sexual interest in mares during their performance career, discouraged from showing spontaneous erection and masturbation, or mishandled during breeding under halter are at risk of libido problems. When exposed to a mare for teasing, stallions such as these may simply stand quietly,

may appear anxious and confused, or may savage the mare.

Most stallions with such experience-related libido problems respond well to behavior therapy alone or in combination with anxiolytic medication. These stallions typically respond best to continued exposure to mares, initially with minimal human presence, and then with gradual introduction of quiet, respectful, patient, positive reinforcement-based handling. These stallions appear to respond favorably to reassurance for even small increments of improvement. Tolerance of minor misbehavior rather than punishment is often the most effective strategy with low-libido stallions. The anxiolytic diazepam (0.05 mg/kg through slow IV 5-7 min before breeding) is useful in about half of such cases as an adjunct to behavior modification.

Some libido problems are hormone-related, with androgens on the low side of the normal range. These stallions will likely improve with management aimed at increasing exposure to mares and reduced exposure to other stallions. This will typically increase androgen levels, general confidence, as well as sexual interest and arousal. Gonadotropin-releasing hormone (GnRH; 50 µg SQ 2 hr and

Furthermore, the researchers suggested that this induction scheme would work only in mares with a mature fetus, and that mares foaling on days subsequent to the initial treatment did not respond to oxytocin because the fetus was not fully mature. This method of induction appears to be a safer but more labor-intensive approach for a field practitioner.

## CONCLUSIONS

In summary, several factors affect the success of induced parturition in the mare. Fetal readiness for birth is paramount to survival of the foal after birth. Critical evaluation of mammary secretion electrolytes, cervical relaxation, and gestational length facilitates proper mare selection and neonatal survivability with induced parturition. Oxytocin is the current agent of choice to induce parturition in the mare. The method of oxytocin administration does not impact neonatal adaptability after induced birth. Because a low-dose oxytocin protocol is effective for inducing parturition in the mare, higher doses of oxytocin are unnecessary and may be inappropriate.

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# CHAPTER 5.30

## Stallion Behavior Problems

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This chapter briefly outlines several of the most common behavior problems of breeding stallions. These problems include self-mutilation, inadequate libido, rowdy breeding behavior, specific erection dysfunction, mounting and thrusting difficulties, frenzied hyperactive behavior, and specific ejaculation dysfunction. Also briefly outlined is the common problem of residual stallionlike behavior in geldings.

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Some libido problems are hormone-related, with androgens on the low side of the normal range. These stallions will likely improve with management aimed at increasing exposure to mares and reduced exposure to other stallions. This will typically increase androgen levels, general confidence, as well as sexual interest and arousal. Gonadotropin-releasing hormone (GnRH; 50 µg SQ 2 hr and



again 1 hr before breeding) can be useful to boost libido in stallions, particularly in those with low normal levels. In rare cases when more rapid improvement is required to rescue a breeding career, treatment with testosterone can effectively jump-start a slow novice without apparent significant adverse effects on spermatogenesis. Current recommendations are 0.1 to 0.2 mg/kg aqueous testosterone SQ every other day for as long as 2 weeks, with frequent assay of circulating testosterone not to exceed 4 ng/ml.

### SPECIFIC ERECTION DYSFUNCTION

Libido-independent erection dysfunction is rare in stallions. The majority of erection dysfunction that does occur is related to traumatic damage of the corpora cavernosa that results in insufficient or asymmetric tumescence (lateral or ventral deviations) that impairs insertion. In some instances, penile injury appears to impair sensory and or proprioceptive feedback from the penis, delaying ejaculation, coupling, or organized thrusting. Common causes include stallion ring injuries, drug-related paralyzed penis and paraphimosis, kick injuries, and self-serve breeding dummy accidents.

An interesting and often confusing type of erection dysfunction involves the folding back of the penis within the prepuce. The behavioral hallmark of this situation is a stallion that appears aroused and ready to mount, without a visible erection. The stallion may also appear uncomfortable or intermittently distracted, pinning the ears, kicking toward the groin, and/or stepping gingerly on the hind legs. Close observation reveals a rounded, full-appearing prepuce, with the skin stretched taut. Resolution usually requires removal of the stallion from the mare until the penis detumescs. Once the penis is fully withdrawn, application of a lubricating ointment to the prepuce facilitates subsequent normal protrusion. This situation tends to repeat occasionally over time, particularly in stallions with profuse smegma production or with dryness of the penis and sheath from frequent cleansing.

### MOUNTING AND THRUSTING DIFFICULTIES

A significant percentage of breeding dysfunction appears to involve neurologic or musculoskeletal problems that affect the stallion's ability to mount and thrust. Many such stallions can continue breeding with therapy aimed to reduce discomfort and accommodate disabilities during breeding, including adjustments to the breeding schedule aimed at reducing the total amount of work. This author has found that long-term treatment with oral phenylbutazone (2-3 mg/kg orally twice daily) often works well to keep such stallions comfortable for breeding. Certain debilitated stallions can benefit from semen collection while standing on the ground.

### SPECIFIC EJACULATION DYSFUNCTION

Although any libido, erection, or mounting and thrusting problem can result in failure to ejaculate, stallions also exist in which the dysfunction seems to be specific to ejaculation. Specific ejaculation problems can include apparent

failure of the neural ejaculatory apparatus, physical or psychologic pain associated with ejaculation, and genital tract pathology. Goals of therapy are to address as many contributing conditions as possible, as well as to optimize handling and breeding conditions and maximize musculoskeletal fitness and libido to enhance the stallion's ability to overcome ejaculatory difficulty. Imipramine hydrochloride (0.5-1.0 mg/kg orally 2 hr before breeding) can effectively reduce the ejaculatory threshold.

### ROWDY BREEDING BEHAVIOR

Rowdy, misbehaved breeding stallions in most cases represent a human-animal interaction problem. Most problems can be overcome with judicious, skillful, respectful re-training. Even strong, vigorous, and misbehaved stallions can be brought under control by using consistent positive and negative reinforcement, with very little or no severe punishment. Re-training can be done in a safe and systematic manner without abuse or commotion, usually within a few brief sessions. Some of the most challenging, rowdy stallions may benefit from vigorous exercise under saddle or ground work immediately before breeding. This practice not only fatigues the stallion but also establishes a pattern of the stallion taking direction from a handler. For similar reasons, this author recommends an intensive schedule for breeding shed retraining, with as many as several breedings per day. With fatigue and reduced urgency to breed, many stallions seem more able to abide direction and learn a routine. With rapid repetition, stallions seem to more readily understand the routine. Tranquilization is generally not recommended. Levels of sedation that improve controllability without compromising musculoskeletal stability or ejaculatory function are difficult to achieve. Tranquilizing agents commonly used in stallions, such as xylazine or detomidine, can both facilitate and inhibit erection and ejaculation depending on dose.

### FRENZIED BEHAVIOR

Distinct from simple rowdiness, some stallions are hyperactive or even frenzied. This is typically greater during the breeding season. Some will spend nearly their entire time budget frantically "climbing the walls," or running a fence line. In general frenzied breeding stallions can benefit from more roughage and less grain in the diet, organized physical work and pasture exercise, and consistent housing in a quiet area. Careful observation (particularly video surveillance) can be useful to identify environmental conditions and events that set off episodes or tend to quiet a stallion. In extreme cases, pasturing directly with mares can effectively quiet or sensibly occupy a frenzied stallion. L-Tryptophan supplementation (1-2 g twice daily in feed) can have a calming effect on such stallions. Tranquilization for this purpose is not recommended in breeding stallions because of risk of paralyzed penis and paraphimosis.

### SELF-MUTILATION

Although not unique to stallions, self-mutilation is a severe and relatively uncommon fertility limiting and/or

life-threatening problem. This behavior typically takes the form of self-biting of the flank, chest, or limbs, with violent spinning, kicking, and vocalization. Self-mutilation in horses appears to occur in two distinct forms. One appears to be a severe reaction to irritation or pain, and would be similar in males or females. The self-biting is typically targeted toward the site of discomfort. Another form occurs in males and is reminiscent of stallion intermale aggression. The behavior is targeted at the typically intermale sites of aggression—the groin, flank, knees, chest, and hocks. The sequence of the behavior follows closely to that of two males fighting, with sniffing and nipping of the groin, vocalization, stamping with a fore leg, kicking out with a hind leg, and then taking occasional larger bites from anywhere on the opponent's body.

Episodes often appear to be stimulated by sight, sound, or smell (feces or oily residues) of another stallion. For some stallions, episodes are set off by sniffing their own excrement or oily residues on stall walls or doorways. Current recommendations to control episodes are as follows: (1) physically protect the stallion from injury by padding walls or limbs, blanketing, and muzzling as effective; (2) aggressively evaluate the housing and social environment to identify exacerbating and ameliorating conditions that may be manipulated for greatest relief; (3) reduce concentrates and increase grass and hay in the diet to increase feeding time and eliminate highly palatable meals (feeding tends to distract and occupy the stallion; concentrate meals tend to increase stereotypic behavior); (4) apply odor-masking agents (Vicks or Acclimate) around the nares; and (5) provide as much organized exercise as possible, also to distract the stallion.

## RESIDUAL STALLIONLIKE BEHAVIOR IN GELDINGS

Castration, regardless of age or previous sexual experience, does not always eliminate stallionlike behavior in horses. If given the opportunity, as many as half of geldings will show stallionlike behavior to mares, many will herd mares, and even mount and appear to breed. Similarly, although castration does tend to “mellow” most horses, it does not eliminate general misbehavior. Traditional behavior modification is usually much more effective in the control of sexual and aggressive behavior in a gelding under saddle or in-hand than it is with an intact stallion. Also, treatment aimed at quieting sexual and aggressive behavior, such as progesterone (e.g., altrenogest, 50-75 mg orally daily), is typically more effective in geldings than in intact stallions. Elimination of stallionlike herding and teasing at pasture is difficult. Separation from mares is recommended.

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## CHAPTER 5.31

# Obstetrics

ROBERT J. HUNT  
*Lexington, Kentucky*

**A**lthough the incidence of dystocia is relatively low (1%-4%), this condition has a marked economic impact on the equine industry. Early recognition of the problem and correct manipulation of the fetus are mandatory to achieve a successful outcome for both the mare and the foal.

Normal parturition is made up of three stages. In the first stage, also referred to as the *preparatory* stage, contractions of the uterus increase pressure on the softened cervix so that it gradually dilates. During this stage the forequarters of the fetus rotate from a dorsopubic to a dorsosacral position. These internal activities often make the mare appear restless and exhibit signs similar to colic.

Stage I typically lasts from 30 minutes to 4 hours and ends with rupture of the chorioallantoic membrane and discharge of the watery allantoic fluid. If the membrane is thickened, for example by fescue toxicity or placentitis, then it may fail to rupture and a red, velvety sac will protrude through the vulvar lips. This premature detachment of the fetal membrane compromises the fetal oxygen supply. The membrane must be ruptured manually and the foal extracted as soon as possible. Care should be taken to ensure that the cervix is fully dilated or it may be torn during forced extraction.

In stage II of parturition the fetus passes into the birth canal enclosed within the amniotic membrane. Normally

life-threatening problem. This behavior typically takes the form of self-biting of the flank, chest, or limbs, with violent spinning, kicking, and vocalization. Self-mutilation in horses appears to occur in two distinct forms. One appears to be a severe reaction to irritation or pain, and would be similar in males or females. The self-biting is typically targeted toward the site of discomfort. Another form occurs in males and is reminiscent of stallion intermale aggression. The behavior is targeted at the typically intermale sites of aggression—the groin, flank, knees, chest, and hocks. The sequence of the behavior follows closely to that of two males fighting, with sniffing and nipping of the groin, vocalization, stamping with a fore leg, kicking out with a hind leg, and then taking occasional larger bites from anywhere on the opponent's body.

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In stage II of parturition the fetus passes into the birth canal enclosed within the amniotic membrane. Normally

the foal's forefeet, covered with amniotic membrane, are the first structures to present through the vulvar lips, followed soon after by the muzzle. This expulsive phase is associated with strong uterine contractions and sometimes violent rolling actions by the mare. The foal is usually delivered within 20 to 30 minutes from the time of rupture of the chorioallantois.

Stage III of labor is characterized by passage of the fetal membranes and initiation of uterine involution. Dystocia is typically associated with prolonged parturition during the first or second stages; an early sign of this condition is excessive straining that is not associated with advancement of the fetus. Early recognition of these problems and appropriate intervention is important for a successful delivery. On large farms dystocia is typically recognized by trained personnel who often have considerable experience managing foaling problems.

### ETIOLOGY OF DYSTOCIA

Dystocia may result from maternal or fetal causes. Maternal-fetal size discrepancy is uncommon in the mare. Pelvic deformity or callous formation may impinge on the birth canal. Other maternal causes include late-gestation uterine torsion, abdominal wall herniation, and rupture of the prepubic tendon. Occasionally the foal's foot or muzzle will create a vaginal or rectal tear. Subsequent straining can cause eventration of the mare's intestine which then prevents passage of the foal. The small intestine, descending colon, or ascending colon may be expelled through the laceration.

Uterine, placental, or fetal infections may result in dystocia because the dead or compromised fetus is not able to make the necessary positional and postural changes required for birth. The most frequently encountered malposition is failure of the fetus to rotate from a dorsopubic into a dorsosacral position—an "upside down" foal. Fetal postural abnormalities may occur with or without anatomic structural aberrations. The most common structural abnormality involves flexural deformities. These deformities typically involve flexion of both forelimbs and occasionally the head and neck as well. A common postural abnormality occurs when a viable fetus retracts its head and neck in response to vaginal intervention by personnel early in the delivery process. The uterine contractions continue to move the fetus into the pelvic canal, thus its head and neck may be displaced laterally, or down between the legs. Although uncommon, twin deliveries are frequently associated with dystocia.

Shoulder or elbow lock at the entry to the birth canal is usually a combination of postural abnormality and maternal-fetal size discrepancy. Hip lock is also typically associated with a maternal-fetal disproportion. Cranial presentation of the foal with one or both rear feet over the brim of the pelvis may be postural but often is associated with some deformity in the fetal hindquarters. Caudal presentation of the fetus is rare (~1%) and is usually characterized by the presence of one or both hind feet at the vulvar lips. Alternatively bilateral hip flexion so that only the fetal tail and rump are palpable at the pelvic brim (breech posture) may occur. A variant of this occurs when there is also bilateral hock flexion. Transverse presentation of the

fetus is extremely uncommon (approximately 1 in 1000 foalings). These cases may be associated with flexural limb deformities, angular limb deformity, spinal deformities, or other miscellaneous anomalies such as hydrocephalus or hydroperitoneum.

### MANAGEMENT OF DYSTOCIA

Materials required to correct a foaling problem may be as simple as an obstetrical sleeve, lubricant, and some baling twine. However it is common practice for a clinician to have on hand a pair of obstetrical chains (or straps) and handles or a Krey-Schotter hook, and a snare rod. Copious lubrication is often the key to success. A fetotome, wire, handles, guide, and a guarded scalpel are necessary to perform a fetotomy. Cleanliness is essential as is a large working area with good footing. The behavior of a foaling mare can be unpredictable and violent, thus safety for all personnel is an important consideration. Ideally the obstetrician should have access to a hospital facility where general anesthesia can be given and an overhead hoist system is available to lift the mare's hindquarters.

The degree of restraint required for a safe examination and fetal extraction will vary with the individual mare. Although placement of a large-bore stomach tube or endotracheal tube into the mare's trachea is reported to reduce straining, this procedure is of little benefit clinically. Application of a nose twitch or other methods of physical restraint offer limited help. Epidural anesthesia will reduce straining in the standing mare but the time needed to obtain an effective block precludes its routine use. Certainly the hindlimb ataxia that can be associated with an epidural is contraindicated if general anesthesia becomes necessary. Short-term xylazine-ketamine general anesthesia may not eliminate straining but will often permit positioning of the mare to facilitate manipulation of the fetus. Inhalation anesthesia will relax the mare and eliminate straining. Clinicians should be cautious about eliminating uterine contractions because they are beneficial to the delivery process after postural abnormalities of the fetus have been corrected.

Often there is insufficient space within the pelvic canal to permit correction of even simple fetal malpostures; thus repulsion of the fetus from the maternal pelvis back into the uterus is usually an integral part of dystocia correction. The degree of uterine contraction will influence the success of this procedure. Distention of the uterus with liquid obstetric lubricant often provides the extra space needed. If the mare is straining excessively, and/or the uterus is tightly contracted, administration of general anesthesia and elevation of the hindquarters is indicated. This method will reduce the amount of intraabdominal pressure on the uterus and permit the fetus to fall away from the pelvic canal. Elevation of the mare's hindquarters allows the obstetrician to work at a more comfortable level and also eliminates the increased abdominal pressure that occurs if the mare is in lateral recumbency.

Because the value of a foaling mare may range from minimal to millions of dollars, it is impossible to be dogmatic about management of an obstetrical case. The economics of each case will play an important part in the decision process as the clinician contemplates the options—fetotomy, ce-

sarean section, manipulation, and vaginal delivery. The breeding future of the mare must be considered because trauma to the genital tract will have an adverse effect on future fertility. Liberal application of lubricant is essential to protect the delicate membranes. Prolonged vaginal intervention is contraindicated in mares, because the cervix is easily traumatized. Slow traction while monitoring cervical stretching is recommended. If the mare is not under general anesthesia it is best to coordinate traction with the mare's expulsive efforts.

## CRANIAL (ANTERIOR) PRESENTATION

Normal fetal delivery is described as cranial presentation, dorsosacral position, with the foal's head and neck resting on the extended forelimbs. The first and foremost rule for correction of postural abnormalities or a malposition associated with cranial presentation is to ensure that the obstetrician has control of the fetal head. Control can be achieved by placing a loop snare around the mandible. Excessive force is contraindicated; the snare is used to gently guide the fetal head through the birth canal.

If the fetus is found in a dorsopubic position, correction can usually be achieved in the standing mare with enough restraint to ensure the clinician's safety. The foal is repelled and rotated manually. Forelimb flexion is a common malposture, and in some instances may be associated with a congenital flexural deformity. If the fetus is small or underdeveloped relative to the size of the maternal pelvis, delivery can be accomplished with one or both carpi flexed, provided that the shoulder and elbow can be extended. Trauma to the genital tract must be avoided. The obstetrician may extend a flexed forelimb by cupping a hand over the hoof and extending the limb into the pelvic canal repelling the fetus and applying pressure on the dorsal surface of the foal's carpus. In more difficult cases a loop snare or obstetrical chain placed around the pastern of the fetus can facilitate this maneuver. This permits an assistant to apply gentle traction on the distal limb while the obstetrician concentrates on repelling the carpus and proximal limb while cupping the fetal hoof to protect the maternal tissues. The use of excessive force in attempts to straighten the limb increases the risk of tearing the uterine wall and/or cervix. If extreme carpal deformity is present then the distal fetal limb may be removed by making a fetotomy cut at the level of the carpal-metacarpal joint.

If the dystocia is caused by shoulder flexion then amputation of the forelimb proximal to the cartilaginous portion of the scapula may be indicated. The skin and superficial musculature must be incised with an obstetrical palm knife in order to properly seat the fetotomy wire. The amputated limb is then removed, and the fetus delivered by traction. If the fetal head and neck are reflected over its back, or deviated ventrally or laterally, correction may be accomplished by grasping the muzzle, or by attaching a loop snare over the muzzle. If the obstetrician is unable to reach the fetus, the head and neck may be removed by a fetotomy cut at the base of the neck. Alternatively, a cesarean section may be performed.

Hindlimb flexion over the pelvic brim ("dog sitting" posture) will prevent fetal passage through the birth canal. It is sometimes possible to grasp the hindfeet and flex the hocks such that the limb/limbs can be repelled back into

the uterus. A loop snare, twitch, or threaded fetotome may be placed around the pastern and then used to repel the foot. Unfortunately this malposture is usually not detected until parturition is advanced to the point that the forelimbs, head, and chest have already been delivered through the birth canal. In these cases fetal repulsion may not be possible and thus there may be insufficient space within the vaginal canal to manipulate the hindlimb. If the obstetrician is unable to grasp and repel the hindfoot from the pelvic canal, a cesarean section should be considered. An alternative to cesarean section is correction of the malposture by insertion of the surgeon's hand through a hysterotomy. Once the surgeon has grasped the trapped limb and repositioned it an assistant can proceed with a vaginal extraction. This technique reduces the potential for abdominal contamination when a partially delivered fetus is repelled and extracted by complete cesarean section. If surgery is not an option, the owner must accept that correction of this type of dystocia by fetotomy is not without risk to the mare. The fetus is transected through the abdomen and the remaining hindquarters are cautiously repelled into the uterus. The exposed vertebral stump is a cause for concern. The hindlimbs are then retrieved and the fetal remnant is delivered in caudal presentation. If the hindquarters are not easily repelled, an alternative approach is to make a second longitudinal hemipelvic fetotomy cut. The fetal parts are then repelled and extracted separately.

## CAUDAL (POSTERIOR) PRESENTATION

If both of the hindlimbs are extended in a caudal presentation, delivery should proceed with steady traction applied to the distal limbs. If the hindlimbs are flexed at the hocks, the fetal rump and proximal hindlimb must be repelled to provide sufficient space for manipulations. A loop snare or obstetric chain will permit an assistant to apply traction to the distal limb while the obstetrician repels the hock dorsally and laterally. The toe of the fetal hoof must be cupped while it is guided medially over the pelvic brim. Although the manipulations are similar, it is usually more difficult to extend a flexed hock than to correct a carpal flexion. The obstetrician should be aware that the hock might cause a dorsal rupture of the uterus when the hoof is being guided over the pelvic brim. Alternatives are a fetotomy cut through the tarsometatarsal joint, or a cesarean section. Bilateral hip flexion posture in caudal presentation (breech) is extremely difficult to correct because of the length of the fetal extremities. If attempted, the malposture must first be converted to a bilateral hock flexion. Alternatives are cesarean section or fetotomy. If fetotomy is attempted, the wire is passed between the hindlimb and trunk, and the head of the threaded fetotome is held firmly against the perineum. Removal of one limb may provide sufficient space to correct the malposture in the remaining limb.

## TRANSVERSE PRESENTATION

Transverse presentation is often associated with fetal deformity, or ankylosis of the hindlimbs. In a ventrotransverse presentation, the forelimbs and hindlimbs may be

located within the pelvic canal. This condition must be differentiated from twins. If a ventrotransverse presentation is detected early it may be possible to reposition the fetus and proceed with a vaginal delivery. Dorsotransverse presentations are even more rare. In both instances cesarean section may be the best option. A multiple-cut fetotomy can be performed, but this procedure is not without risk to the mare's future fertility.

### CESAREAN SECTION

Surgery should be performed when a live foal is present and its size, posture, position, and/or presentation make a safe vaginal delivery impossible. Cesarean section may be required in the case of severely deformed foals with non-correctable postural abnormalities to avoid excessive trauma to the mare. Common approaches for cesarean section in the mare include ventral midline and low flank or paracostal. The low flank or paracostal approach is used if excessive ventral edema is present, and is also the approach of choice in the field when the intent is to rapidly retrieve the foal followed by euthanasia of the mare. The ventral midline approach is used most commonly in a hospital setting. If the fetal membranes are detached, they are removed. However, the membranes are most often still attached, and they are manually stripped 3 to 4 cm from

the edge of the hysterotomy incision to prevent incorporation in the closure of the uterus. In the past a continuous "whipstitch" has been placed around the perimeter of the incision to control postsurgical intrauterine hemorrhage. This whipstitch was then followed by a two-layered closure. A more efficient alternative is to eliminate the perimeter whipstitch and use a Ford interlocking layer for the initial closure, followed by an inverting layer of the surgeon's choice.

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## CHAPTER 5.32

# Evaluation of the Postpartum Mare and Neonate

DAVID G. HARRIS  
*Paris, Kentucky*

**E**valuation of the postpartum mare and neonate begins with collection of historic data, followed by observation of the mare and foal at ease, physical examination of the neonate, physical examination of the mare and, finally, examination of the fetal membranes. This order of examination follows a path from least contaminated to most contaminated and helps protect the health of the neonate at this vulnerable time. The initial veterinary examination is usually performed in the morning, often 8 to 12 hours after birth. A second evaluation 24 hours later is sometimes indicated. The physical examinations should be thorough but also performed in a manner that does not interrupt the adaptation processes that are underway. Information collected about the mare and the foaling process, as well as findings from the physical examination of the mare, neonate, and fetal membranes, will indicate whether a therapeutic plan is appropriate.

Emphasis should be on prevention and early detection of disease processes.

### FOALING HISTORY

Knowledge of the mare's previous foaling history may be beneficial in preparation for delivery. When gathering a history, the clinician's goals are to prevent problems if possible and to be well prepared for any complications that may occur. The history begins with information about any behavioral problems, medical problems, immune-mediated problems, or any injury that may affect the delivery of a healthy foal. Extremely aggressive mares require special attention to prevent injury to the foal, handlers, or the mare herself. Medical problems that could affect foaling include fevers, nutrition, infections, metritis, placentitis, lactation problems, condition of the mare,

located within the pelvic canal. This condition must be differentiated from twins. If a ventrotransverse presentation is detected early it may be possible to reposition the fetus and proceed with a vaginal delivery. Dorsotransverse presentations are even more rare. In both instances cesarean section may be the best option. A multiple-cut fetotomy can be performed, but this procedure is not without risk to the mare's future fertility.

### CESAREAN SECTION

Surgery should be performed when a live foal is present and its size, posture, position, and/or presentation make a safe vaginal delivery impossible. Cesarean section may be required in the case of severely deformed foals with non-correctable postural abnormalities to avoid excessive trauma to the mare. Common approaches for cesarean section in the mare include ventral midline and low flank or paracostal. The low flank or paracostal approach is used if excessive ventral edema is present, and is also the approach of choice in the field when the intent is to rapidly retrieve the foal followed by euthanasia of the mare. The ventral midline approach is used most commonly in a hospital setting. If the fetal membranes are detached, they are removed. However, the membranes are most often still attached, and they are manually stripped 3 to 4 cm from

the edge of the hysterotomy incision to prevent incorporation in the closure of the uterus. In the past a continuous "whipstitch" has been placed around the perimeter of the incision to control postsurgical intrauterine hemorrhage. This whipstitch was then followed by a two-layered closure. A more efficient alternative is to eliminate the perimeter whipstitch and use a Ford interlocking layer for the initial closure, followed by an inverting layer of the surgeon's choice.

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abortions or stillbirths, previous septic foals, retained fetal membranes, previous colic or colic surgery, and previous dystocias or difficult deliveries. Immune-mediated problems would include failure of passive transfer and previous neonatal isoerythrolysis foals. Injuries of the pelvis that affect the size of the birth canal, perineal and vaginal lacerations, rectovaginal tears, and cervical tears may affect the management of the delivery. This historic knowledge will help to increase the likelihood that the birth will be trouble-free, with the delivery of a healthy foal and a mare that will conceive readily for the next season.

## NORMAL PERIPARTUM PROCEDURES

The expected foaling date should be calculated as 11 months and 5 days. At approximately 30 days before foaling, booster vaccines should be given and the mare should be dewormed. If fescue toxicosis is problematic in the area, foaling mares should not be allowed to graze fescue pasture and should not be fed hay-containing fescue within 30 days of foaling. Domperidone may be given in a daily oral dose of 1.1 mg/kg, beginning 15 days before the anticipated foaling date if the threat of fescue toxicosis cannot be removed.

Weather permitting, foaling can take place outside in a grassy paddock. The mare should not be allowed to foal in the presence of other mares. If a foaling stall is used it must be prepared by thorough cleaning and disinfection. Cleaning is the first step and a detergent must be used to disperse the lipid biofilm layer that may protect some pathogens. After the stall has dried, an approved phenolic disinfectant should be used to soak all surfaces within the stall. Feed tubs and water buckets should be cleaned, rinsed, and allowed to dry before placing them back in service.

Then 2 weeks before foaling, the mare's perineal area should be examined for conformation; the Caslick's procedure should be opened if necessary. Signs of previous injury or tears may indicate that additional care is needed at parturition to avoid repeat foaling injuries.

On most large farms there will be a nighttime foaling attendant. This individual is trained to watch for the signs of stage 1 labor and then wrap the tail with gauze, tape, palpation sleeve, or some combination of these items, and wash the udder and perineal area with cotton soaked in a weak solution of water and povidone iodine scrub. A detergent is necessary in the scrub to break the lipid layer on the skin. The scrub should be rinsed off with water. After delivery, the umbilical cord is held close to the foal's abdomen as the cord breaks, and the umbilical stump is immediately dipped in, or sprayed with, a navel dip solution. The application of navel dip solution is repeated again in 4 to 6 hours. Navel dip solutions such as 7% iodine are tissue destructive and should be avoided. Iodine-based solutions at 2% to 3.5%, povidone iodine solution at 2%, or chlorhexidine solution at 0.5% will reduce bacterial numbers without destroying tissue. Chlorhexidine scrub and povidone iodine scrubs have been used successfully as navel dips.

The newborn foal should be vigorously scrubbed with a towel to stimulate the foal's movements and respirations. Then the mare and neonate should be observed from a distance for signs of normal or abnormal behavior. After

the mare stands, the colostrum's specific gravity should be tested to estimate quality. A specific gravity of 1.06 or greater is adequate. If the Eclipse refractometer is used a reading of 23% corresponds to a specific gravity of 1.06. It is good practice to collect a pint to freeze if quality is high. Colostrum with a specific gravity of 1.06 will have an approximate immunoglobulin (Ig) concentration of 3000 mg/dl. If the specific gravity of the colostrum is low, then 1 g of colostrum IgG/kg of birth weight should be given by oral supplementation.

The soiled bedding should be removed and replaced with clean dry bedding. The mare and foal should still be observed for normal behavior. The foal should be in a sternal posture within 1 to 2 minutes, and a suckle reflex should be present within 2 to 20 minutes. Standing should occur within 2 hours, and the foal should nurse by 3 hours after birth. Once nursing has occurred the foal may be given a warm water or soap-based enema to facilitate passage of the meconium. Commercial phosphate enemas may be used, but repeated use should be avoided because of the absorption of the phosphate ion. If vital signs are taken, the foal's temperature should fall in the range of 99° to 101.5° F (37.2°-38.6° C), the heart rate at 1 to 5 minutes should be greater than 60 beats per minute (bpm), and at 5 to 60 minutes it should be 80 to 130 bpm. The respiratory rate is high initially at 60 to 80 bpm in the first 30 minutes and then drops to 30 to 40 bpm within 1 to 12 hours after birth.

## EVALUATION OF THE NEONATE

The first veterinary examination should occur within the first 24 hours of birth. The clinician should begin by observing from a distance with the mare and neonate at ease to evaluate the foal's attitude, ability to rise, ability to nurse, coordination, and strength. Next the clinician should perform a complete physical examination that includes checks of the eyes, temperature, mouth and mucous membranes, heart and heart rate, lungs and respiratory rate, ribs, umbilicus, perineum, and limb conformation.

Blood can be drawn for the evaluation of the blood IgG level at 8 to 12 hours postfoaling. A blood level of 800 mg/dl or greater is adequate and no supplementation is necessary. An IgG blood level of 400 mg/dl or less indicates failure of passive transfer. This low level requires immediate oral supplementation with frozen colostrum or a commercial oral supplement. At least 250 ml of colostrum with a specific gravity of 1.06 or greater should be given by nasogastric tube. The foal's IgG blood level should be retested in 24 hours and therapy reevaluated. If the foal is more than 24 hours old and has a low IgG blood level, 1 L of plasma should be administered IV. This plasma may be from a suitable donor or a purified commercial product may be used. A suitable donor must have a compatible blood type determined by cross match (see Chapter 6.7 "Blood and Blood Component Therapy"). Broad-spectrum antibiotic therapy should be initiated because these foals are at risk for infection.

In selected cases additional diagnostics, including a complete blood cell count (usually taken with the IgG blood level), chemistry profile, radiography and ultrasound examination, may be indicated.



## EVALUATION OF THE POSTPARTUM MARE

Evaluation of the mare begins with distance observation of the dam and foal at ease in the stall. The mare should display normal adaptive behavior. Abnormal behavior patterns are discussed in Chapter 5.15. A complete physical examination should include evaluation of the mucous membranes for signs of hemorrhage, eyes for abrasions, heart and heart rate, lungs and respiratory rate, mammary development and colostrum production, and especially the perineal area. Close observation of the perineal area for injuries, swelling, bruising or discharge is crucial at this time to determine if therapeutic intervention is necessary for the mare. The colostrum should be gray to yellow in color, thick and sticky. Management of fetal membrane retention is discussed in Chapter 5.35.

Lavage of the uterus of the mare postpartum can be both therapeutic and diagnostic. This procedure can be easily performed 24 hours after foaling by using saline warmed to body temperature and a lavage tube. As few as 2 or as many as 10 L of saline may be needed to effectively lavage the uterus. Indications for lavage would include dystocias or difficult labor, old age, vaginal discharge, inability to be turned out in a paddock for exercise, or fetal membrane retention. The practitioner should perform abdominocentesis to be confident that there is no uterine tear present (see Chapter 5.23: "Peritoneal Fluid"). At the time of the second visit, usually 48 hours postpartum, a Caslick's procedure may be performed if indicated.

## EVALUATION OF FETAL MEMBRANES

Although the fetal membranes are evaluated last, they can provide a great deal of information that may change the entire approach to treatment and management of the mare and neonate. The foaling attendant should collect the fetal membranes as soon as possible after expulsion and place them in a bucket to be weighed and protected until the attending veterinarian can examine them. As a guideline, the fetal membranes should weigh approximately 11% of the body weight of the foal at birth.

The gross examination of the fetal membranes should be performed on a flat surface in a well-lighted area. The membranes are normally passed inside out; thus the allantoic surface is examined first. The membranes, with the allantoic surface exposed, should be placed in the shape of the letter F—with the cervical star at the bottom, the

gravid horn at the top, and the nongravid horn in the middle. The entire allantoic surface should be inspected for any gross abnormalities or tears. Tears of the chorioallantoic membranes may have resulted from being stepped on by the mare or some other trauma. It can be difficult to determine whether a piece of the membrane is missing and is retained in the uterus of the mare. Alignment of blood vessels can be useful to confirm whether a tear is present, or a piece of membrane missing.

The examination should continue with inspection of the amniotic membranes and umbilical cord. The umbilical cord normally has a few twists; the length of the umbilical cord should approximate the length of the body of the uterus. The twists in the umbilical cord result from fetal mobility during gestation, and in extreme cases can lead to vascular compromise and asphyxiation. Excessive length of the cord has been associated with entrapment of limbs or trunk, and vascular compromise. Short cords may lead to premature rupture of the cord during delivery and fetal hypoxia.

Next the fetal membranes should be inverted through the cervical star so that the red, velvety chorionic surface is exposed. The membranes should be spread out and placed in the shape of the letter F again. The chorionic surfaces should be inspected for any abnormalities such as tears, discoloration, thickening, exudate, avillous areas. Exudates indicate placentitis that can lead to placental insufficiency and fetal asphyxia.

Careful evaluation of the fetal membranes will give the practitioner information about the uterine environment during late gestation. If needed, therapy for the mare and/or neonate may be indicated to prevent serious complications.

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## CHAPTER 5.33

# Postpartum Prolapse and Genital Tract Lacerations

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### UTERINE PROLAPSE

The veterinarian can be presented with a case of uterine prolapse under two conditions. The first is the prolapse that occasionally occurs under general anesthesia when the mare is in dorsal recumbency. The second is the prolapse that occurs during natural foaling. The former type of prolapse usually is associated with delivery of the fetus; it is secondary to the abortion or delivery and probably occurs because of the positioning and the relaxation of anesthesia. The uterus is usually undamaged by the prolapse and is easily replaced. The surgery table should be tipped to aid in the replacement of the uterus and towel clamps are often placed in the vulva. Once the mare recovers, re prolapse is usually not a problem; however, the uterus should be lavaged with sterile fluid to allow complete reduction of any horn eversion. Oxytocin should be given intramuscularly to assist in uterine involution.

Prolapse also occurs during foaling. Uterine prolapse associated with foaling is an emergency. At a minimum, the uterus can be severely damaged with negative effects on future fertility. It is not uncommon for a mare to hemorrhage sufficiently, usually from a uterine artery rupture, to die from hypovolemia. The prolapsed uterus should be protected, and suspended if possible, until it can be replaced. This author prefers general anesthesia for uterine replacement because it provides optimal control and relaxation of the mare, and it is a safer procedure for the personnel involved. Although anesthesia is a greater risk for the mare, this author believes that the benefits outweigh the risks.

The uterus must be cleaned and then replaced through the cervix. Topical treatments to remove uterine edema have not been useful in this author's experience. Lubrication of the uterine tissues and manual compression seem to provide the most benefit. Obstetricians should be aware that during replacement it can often seem as though not much progress is being made, and then the uterus will seem to fall in place all at once. Persistence is the key to uterine prolapse replacement. Lavage and oxytocin should be provided as indicated above once the mare recovers from anesthesia.

### RECTAL PROLAPSE

Irritation to the anus that can result in straining and subsequent rectal prolapse is unusual after foaling but can occur. Most rectal prolapses are relatively short and result in

a rather gruesome, doughnut-shaped mass of bloody tissue that protrudes from the anus. If the feces are soft enough, most mares can pass some fecal material through the prolapse. However, the appearance of the prolapse, and the associated straining, may necessitate surgical treatment under epidural anesthesia.

The clinician removes the edematous and hemorrhagic tissues by sharp dissection, leaving enough mucosa and submucosa to circumferentially suture without tension. Because the cranial rectum pulls orally once the edematous tissue is removed, the prolapse should be dissected free and then closed in quarters. This method facilitates exposure of the anastomosis site for the first three quarters of the circumference. Oral laxatives such as mineral oil and a nonsteroidal antiinflammatory will facilitate fecal passage. Short-term use of antimicrobials is at the surgeon's discretion.

### RUPTURE OF THE SMALL COLON MESENTERY

Rupture of the mesentery of the small colon can occur during parturition—after either rectal prolapse or an apparently normal foaling. Stretching of the mesentery during parturition tears the distal small colon mesentery from the bowel for a varying length. Rupture of the small colon mesentery can be difficult to diagnose. Clinical signs associated with the rupture can be delayed for 24 to 48 hours after foaling. The first clinical sign is the failure of the mare to pass feces after foaling, followed by a low-grade fever (102°–103° F; 38.9°–39.4° C) and, finally, bloating. Low-grade signs of colic can be seen at any time during this period. An impaction of the distal small colon can be palpated per rectum if the damage involves the distal small colon. Differential diagnoses include uterine rupture and septic metritis.

Ultrasound and abdominal paracentesis can be very beneficial in diagnosis. Uterine ruptures tend to have large volumes of abdominal fluid with elevated white cell counts and can resemble lochia. Within the first 24 hours after foaling, mesenteric ruptures have smaller amounts of blood in the peritoneal cavity and little evidence of peritonitis. With time, however, the damaged bowel leaks bacteria and the abdominal fluid reflects the infectious nature of the problem.

Mesenteric ruptures that result in compromised bowel require surgery. Repair of the damage is limited by the

surgeon's ability to access the distal aspect of the mesenteric tear. If the damage extends into the pelvic canal, euthanasia is necessary. If a healthy bowel can be reached at the distal limit, resection and anastomosis of the damaged bowel should be performed. A relaxed abdominal wall after parturition, a large ventral midline incision, removal of the large colon from the abdomen, and tilting the head of the surgery table forward can improve access to structures in the caudal abdomen. The small colon is transected at the distal limit of the damage. The compromised bowel is removed from the abdomen and is used as a conduit to relieve the small-colon impaction in the damaged section and in the bowel oral to the damage. After a sufficient amount of ingesta is removed to allow anastomosis, an end-to-end, hand-sewn, double inverting closure of the small colon is performed. The mesentery that is visible should be closed with a simple continuous pattern. Closure of the deeper mesentery should be performed, but it cannot be seen. Deep mesenteric closure is performed by using absorbable suture material on a large-taper, half-circle needle in a simple continuous pattern. Closure of the mesentery close to the dorsal body wall is performed first. The dorsal knot is made either by using a double strand of suture and looping the needle through the two strands after placing the first bites, or by one-handed tie. By placing traction on the distal mesentery, the surgeon can palpate both sides of the rent in the abdomen and suture using one hand. A moistened lap sponge under the mesentery ensures that bites will grab the sponge and not the adjacent bowel. Before closure of the abdominal wall, the colon should be emptied through pelvic flexure enterotomy if a large amount of ingesta is present. Emptying will reduce the volume of feces that must immediately pass through the anastomosis.

Postoperatively, the mares are kept off of water for 24 to 36 hours and hay for 36 to 48 hours. Intravenous (IV) fluids are necessary for hydration. Mineral oil is administered through nasogastric tube before feeding to help soften the feces and avoid stomal impactions. Perioperative antimicrobials such as penicillin and gentamicin are recommended. Postoperative complications are common after repair of small-colon ruptures, and include colic, colitis, adhesions, and peritonitis.

### BLADDER EVERSION

Bladder eversion also occurs as a result of straining of the urogenital tract. The everted surface of the bladder is covered with urothelium and is textured. If enough bladder is everted, the openings of the ureters can be seen at the cranial aspect of the everted tissue. To replace it, the bladder must be manually inverted back through the external urethral sphincter. The bladder is first cleansed and then is compressed between the surgeon's hands and slowly pushed through the sphincter. Water-soluble sterile lubricants are very helpful, as is massage of the bladder to remove edema. If patient massage is unsuccessful in replacing the bladder, the external urethral sphincter can be transected dorsally to allow replacement. The incision must be closed to help keep the bladder from re-everting. The bladder should be lavaged with sterile fluid to ensure it is fully replaced and administration of antimicrobials

with urinary excretion and a nonsteroidal antiinflammatory drug is recommended for several days.

### BLADDER PROLAPSE

Intact bladders prolapse as a result of a defect in the peritoneum and vaginal wall. This injury is the result of severe vaginal trauma. The bladder surface will be shiny, smooth, and white with visible subperitoneal vessels. The prolapsed bladder should be cleaned, and the bladder can be drained of urine by aspiration before replacement in the abdomen. A Foley catheter is then placed to keep the bladder decompressed. Urine drainage from the catheter will also reduce urine spillage into the vagina and subsequent contamination of the peritoneal cavity through the rent in the vaginal wall. Treatment of the vaginal wound involves reduction of further peritoneal contamination and prevention of eventration. The vaginal wound heals best by second intention. A cross tie can be used to prevent the mare from lying down; the possibility of eventration is thus reduced. Systemic antimicrobials should be administered.

### BLADDER RUPTURE

Bladder rupture can occur either before, or more commonly after, foaling. The resulting uroperitoneum results in elevated serum levels of creatinine, blood urea nitrogen, and potassium, and lowered concentrations of sodium and chloride. Confirmation of urine in the abdomen makes the diagnosis, and the rent can be observed by an endoscopic examination of the bladder. Medical therapy requires urine drainage and correction of electrolyte abnormalities. Surgical access to the tear is impossible through a celiotomy, so reports of access for surgical repair of bladder ruptures are limited to either a colpotomy approach or to eversion of the bladder through the urethral sphincter. Both surgical procedures are technically demanding, as is a laparoscopic approach, which is unreported but may be possible in some instances. Conservative therapy for bladder rupture is successfully used in many species and may be of value in the mare. Medical therapy must be instituted, and the bladder is kept decompressed by the use of a self-retaining catheter such as a Foley.

### VAGINAL LACERATIONS

Vaginal lacerations associated with eutocia are rare. When present, these lacerations are usually linear defects in the vaginal mucosa that heal by second intention and require no treatment. Occasionally an older mare will rupture a vaginal varicocele and cause hemorrhage. This injury is usually self-limiting, and treatment is unnecessary. Dystocias can cause severe vaginal lacerations, and their extent is dependent on the amount of vaginal trauma. The most common severe vaginal laceration is seen in primiparous mares when damage has occurred to the transverse urethral fold. The entire fold can be torn off or undergo necrosis, resulting in an incompetent external urethral sphincter. This laceration can result in urinary incontinence, scalding, and urine pooling. Immediate treatment

for vaginal lacerations is gentle cleansing of the wounds, the use of a nonsteroidal, antiinflammatory drug, and topical emollients to reduce scarring and adhesion formation. Corticosteroids can be added to the topical medication to also reduce inflammation. Systemic antibiotics are indicated for mares with multiple or deep lacerations. Wounds are allowed to heal by second intention.

In mares with extensive vaginal adhesions or incontinence, surgical therapy is indicated after the wounds have healed. Both conditions have a guarded prognosis. The difficulty with treatment of vaginal adhesions is that they frequently reform. These adhesions seem to be most common in Miniature Horse mares, possibly because of the small pelvic canal in this breed, and the domed head of the fetus predisposes Miniature Horse mares to vaginal trauma. Sharp resection of adhesions followed by topical ointments with steroids may be beneficial. A vaginal vault-sized, soft tampon that is coated with ointment can be used to keep transvaginal adhesions from reforming.

Incontinent mares should have their caudal urethral sphincter pressure augmented. Because these horses are incontinent because of scarring and tissue loss, this procedure can be very challenging. Surgery should be considered only after all inflammation has subsided. The goal is usually to recreate a transverse urethral fold, as well as to extend the urethra in a similar manner to that performed to correct urine pooling.

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## CHAPTER 5.34

# Postpartum Hemorrhage

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**P**ostpartum hemorrhage in the broodmare is not an uncommon problem. Most mares that bleed do so within 12 hours after foaling; however, it is important to remember that a mare may develop a hemorrhage at any time during gestation or even days after parturition. Mares that have suffered a rupture of a major blood vessel of the reproductive tract are often found dead. Others may be discovered moribund and in shock. Many mares that are presumed to be experiencing postfoaling "discomfort" are actually bleeding internally.

Several conditions have been postulated to predispose the mare to arterial rupture. Increasing age, especially in mares that have been gravid every year, leads to uterine vessels that are repeatedly cycled through stretching and contracting. A decrease in serum copper levels has been linked to reduced collagen production and thus vessel fragility. Vessel rupture usually involves the uterine artery, but the ovarian and iliac arteries may also be affected. Dystocia, whether caused by a large foal or some malpresentation, malposition, or malposture, often requires aggressive intervention that can wreak havoc on the reproductive tract. Some farm managers speculate that mares that foal while standing may force the foal's rear hooves up against the taut broad ligament apparatus. However, a presenting patient more than likely will be relatively young and naïve to any of the aforementioned criteria.

It is estimated that in central Kentucky every spring hundreds of mares silently hemorrhage into one or both of their broad ligaments without untoward complications. Approximately 15 to 20 abdominal hemorrhages are referred to this author's hospital facilities, and twice that number may be treated at the farm in the ambulatory setting. The decision to transport a mare that has hemorrhaged into the broad ligament is not without risk, because sudden movement may result in a fatal hemorrhage into the abdominal cavity. The aggressive approach outlined in this chapter requires prior preparation and can be expensive for the mare's owner.

### EMERGENCY KIT

Time is of the essence when diagnosing and treating a hemorrhaging mare. Prior preparation and organization are mandatory, especially if the mare is to be attended to at the farm. Table 5.34-1 provides a list of readily available and essential supplies needed to aid in the resuscitative effort. If the possibility exists that whole blood transfusion would be attempted on site, the additional items listed in Table 5.34-2 also will be needed. All of these items, other than the ultrasound machine, can be kept in a large, sturdy plastic container that is readily accessible for an emergency situation. The container can serve a dual

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Postpartum hemorrhage in the broodmare is not an uncommon problem. Most mares that bleed do so within 12 hours after foaling; however, it is important to remember that a mare may develop a hemorrhage at any time during gestation or even days after parturition. Mares that have suffered a rupture of a major blood vessel of the reproductive tract are often found dead. Others may be discovered moribund and in shock. Many mares that are presumed to be experiencing postfoaling "discomfort" are actually bleeding internally.

Several conditions have been postulated to predispose the mare to arterial rupture. Increasing age, especially in mares that have been gravid every year, leads to uterine vessels that are repeatedly cycled through stretching and contracting. A decrease in serum copper levels has been linked to reduced collagen production and thus vessel fragility. Vessel rupture usually involves the uterine artery, but the ovarian and iliac arteries may also be affected. Dystocia, whether caused by a large foal or some malpresentation, malposition, or malposture, often requires aggressive intervention that can wreak havoc on the reproductive tract. Some farm managers speculate that mares that foal while standing may force the foal's rear hooves up against the taut broad ligament apparatus. However, a presenting patient more than likely will be relatively young and naïve to any of the aforementioned criteria.

It is estimated that in central Kentucky every spring hundreds of mares silently hemorrhage into one or both of their broad ligaments without untoward complications. Approximately 15 to 20 abdominal hemorrhages are referred to this author's hospital facilities, and twice that number may be treated at the farm in the ambulatory setting. The decision to transport a mare that has hemorrhaged into the broad ligament is not without risk, because sudden movement may result in a fatal hemorrhage into the abdominal cavity. The aggressive approach outlined in this chapter requires prior preparation and can be expensive for the mare's owner.

### EMERGENCY KIT

Time is of the essence when diagnosing and treating a hemorrhaging mare. Prior preparation and organization are mandatory, especially if the mare is to be attended to at the farm. Table 5.34-1 provides a list of readily available and essential supplies needed to aid in the resuscitative effort. If the possibility exists that whole blood transfusion would be attempted on site, the additional items listed in Table 5.34-2 also will be needed. All of these items, other than the ultrasound machine, can be kept in a large, sturdy plastic container that is readily accessible for an emergency situation. The container can serve a dual

Table 5.34-1

**Items in an Emergency Kit for Treatment of Postpartum Hemorrhage (Fluid Administration and Diagnosis)**

Items	Minimum Number	Source
12- to 14-Gauge, 6-inch Teflon catheters	Several	Mila Int., Florence, Ky.
Suture, cloth tape, and multiple-puncture catheter caps	Several	
Primary IV sets, 72-inch	4	Abbott Laboratories, Chicago
Hypertonic saline, 950 ml in rigid plastic bottles	Several	
Polyionic crystalloid, 1000 ml in rigid plastic bottles (e.g., Eleetrosol-R, Normosol-R)	12	Abbott Laboratories, Chicago
Rubber pressure bulbs (hand pumps to pressurize fluid containers)	4	
Blood Set with filter for plasma or whole blood administration	4	Lake Immunogenics, Ontario, N.Y., or Veterinary Dynamics, San Luis Obispo, Calif.
Regular plasma, 950 ml		
Ultrasound machine with 5.0-MHz linear probe		
Isopropyl rubbing alcohol	2 pints	

Table 5.34-2

**Items Required for Blood Collection and Administration**

Items	Minimum Number	Source
10-Gauge, 3-inch polypropylene catheters	Several	Jorgenson Laboratories, Loveland, Colo.
Primary IV sets, 72-inch	Several	
Heparin sodium, 1000 unit/ml (6 ml per 2-L blood collection bottle)	Three 10-ml vials	
Evacuated 2-L, blood-collection bottles	4	Baxter Laboratories, Deerfield, Ill.
Blood Set with filter	Several	Baxter Laboratories, Deerfield, Ill.

IV, Intravenous.

purpose by providing a warming tub for fluids when filled with hot water. Extra initiative may be needed to obtain some of these provisions, but it will save precious minutes when they count.

## PHYSICAL EXAMINATION

Unremitting signs of colic in the postfoaling mare warrant a thorough examination by a veterinarian. The restlessness may be caused by uterine contractions, especially if oxytocin has been administered to promote passage of the fetal membranes. If the discomfort continues, however, the possibility of a dissecting hematoma in the broad ligament must be considered. If at any time the pressure causes the ligament to tear, blood can flow freely into the abdominal cavity.

Clinical signs associated with hemorrhage can vary greatly from mare to mare (Table 5.34-3). Most will exhibit colicky behavior to varying degrees, but some will be stoic. The unpredictable and dangerous behavior of many of these mares, along with the fact that most have a viable and newly ambulating foal, make it imperative that at least one, if not more, competent handlers be present. If manpower permits, a very small enclosure can be con-

structed of straw bales outside the stall door allowing safety of the foal and comfort to an anxious mare.

It bears restating that treatment of a mare in hemorrhagic shock involves expedience and a concert of activities going on at once. Thus, diagnosis and treatment usually occur simultaneously. After the initial physical examination, if hemorrhage is presumed, vascular access needs to be established and preliminary fluids started. Handlers can usually take care of the latter while the veterinarian continues with further diagnostics, such as ultrasound. In this day of evaluation of ovarian follicular growth and 14-day pregnancies, many practitioners are privileged to have at their disposal ultrasound machines with a 5.0-MHz linear rectal probe. Although a 3.0-MHz probe is preferable, the 5.0 rectal probe can be used to evaluate a mare's abdomen for signs of hemoperitoneum. Blood will appear hypoechoic and swirling of the cellular elements may be seen. Palpation per rectum and an internal ultrasound exam are discouraged because manipulation in this area can cause further problems. Application of a twitch to these mares can cause even more agitation, not to mention that placing an arm in a distressed mare is even more dangerous than bending down to scan an abdomen. If no fluid is seen with the transabdominal exam-

**Table 5.34-3**  
**Clinical Signs of Postpartum Hemorrhage**

Clinical Signs	Comments
Mental status	Agitated Restless Delirious
Pain and associated signs	Rolling or curling of upper lip Frequent standing up and lying down "Stomping" at abdomen with hindlegs In author's experience, less pawing and rolling than is seen with bowel problems such as large colon torsion
Mucous membranes	Gums often severely blanched Capillary refill undetectable
Skin	Coldness Clammy feel Sweating
Jugular distensibility	Increased jugular fill time (may be difficult to place an IV catheter)
Pulse character	May not even be detectable at facial artery
Heart rate	Usually tachycardic in the range of 80-100+ bpm Possibly normal
Rectal temperature	Frequently <95° F
Respiration	Usually increased and labored; a reflection of metabolic acidosis

IV, Intravenous; bpm, beats per minute.

ination, it can be assumed that the hemorrhage is contained within the broad ligament or uterine wall. Symptomatic treatment for these mares should continue. If fluid is seen, abdominocentesis is highly recommended to differentiate between other possible diagnoses including colon rupture, uterine tear or rupture, or mesenteric tear with hemorrhage and possible spillage of gut contents.

#### ALGORITHM FOR EMERGENCY TREATMENT OF HEMORRHAGE IN THE BROODMARE

A simplified, step-by-step, sample flow chart for hemorrhage treatment is outlined below. The clinician should keep in mind that this outline describes an attempt to treat what should be a surgical problem, medically. One can only surmise at the nature of the internal insult. Periodic evaluation of the mare without quantification of the severity of the internal blood loss and the benefit of blood pressure measurements makes this a very challenging situation.

1. Obtain initial vital signs.
2. If internal bleeding is suspected and the mare is hypovolemic, insert a large-bore (12- to 14-gauge) IV catheter into the left, or most easily accessible,

jugular vein. It may be prudent to catheterize both jugular veins, as these mares change positions frequently and because violent head movement may dislodge a catheter.

3. Administer 2 to 3 L of warmed hypertonic saline. Warmed saline has been shown not only to provide plasma expansion, but also to exert some cytoprotective properties by attenuating harmful humoral cascades.
4. Follow hypertonic saline with 2 to 3 L of a warmed polyionic crystalloid such as Normosol-R or Plasmalyte. These solutions contain readily available buffers such as acetate and gluconate that do not need to be converted by the liver. They are available in rigid plastic containers that can be pressurized by a hand pump. This small amount of crystalloid furnished will often calm and stabilize a mare. The goal is to volume expand just enough to deliver oxygen and nutrients to cells, yet not to elevate blood pressure so that it will dislodge what hopefully is a growing clot at the site of injury. The clinician should not become overzealous in fluid administration without reevaluating vital parameters.
5. Try to make the mare's environment conducive to clot formation (i.e., lessen noise and distractions, create warmth with heat lamps and blankets if it is severely cold), provide water to drink at regular intervals and in appropriate amounts, and if the mare is lying down, let her continue to do so because this may provide some pressure on internal organs and help to stem hemorrhage.
6. Attempt to characterize the site and magnitude of blood loss to better assess the time and expense that may be involved in a continued resuscitative effort. If fluid is found on transabdominal ultrasound, abdominocentesis and fluid analysis is strongly advised.
7. After the initial crystalloids, 3 to 4 L of plasma are highly recommended because they will provide proteins and clotting factors. If owners are willing to spend money and the mare is valuable, plasma is probably the most important "medication" to give. This colloid can be kept in the freezer at home so that it is convenient to take to an emergency, or have it picked up by a farm employee. Thawed plasma can be kept in a refrigerator or cooler for as long as 7 days or more.
8. Reevaluate vital signs and determine if more fluids should be given. A stall-side chart to jot down the course of medications and the amounts administered is highly recommended.
9. Consider taking a peripheral blood sample for complete blood count and biochemical analysis.
10. If the mare continues to deteriorate, serious consideration should be given to a fresh whole blood transfusion (see Table 5.34-2). The main purpose of the transfusion is to provide more oxygen carrying red blood cells. Even though a conservative amount of anticoagulant is prescribed in this protocol, the risk that progression of clot formation could be hindered is always present. A vaccinated, equine infectious anemia-negative gelding or nonparous mare is a suitable donor.

The additional expense of the following adjunctive medications may be deemed necessary once the mare has stabilized:

1. *Aminocaproic acid*—a hemostatic agent to inhibit fibrinolysis; 20 g in fluids can be given as a loading dose, followed by 10 g every 6 hours thereafter; usually started if mare is stabilized, because clot fibrinolysis should not begin until 12 hours after its formation.
2. *Flunixin meglumine*—to control inflammation and endotoxin insult; follow appropriate dosage and regimen.
3. *Furosemide*—to promote enhanced renal blood flow in the face of aggressive resuscitation; follow appropriate dosage and regimen.
4. *Various tranquilizers*—to calm uncontrollable mares; this author avoids these and has not found one to be better than another. A sudden drop in blood pressure may occur in a hypovolemic mare.
5. *Broad-spectrum antibiotics*—sulfonamides or penicillin/gentamicin strongly encouraged if the mare is hydrated.

### Supplemental Readings

Kirby RR, Taylor RW, Civetta JM: Handbook of Critical Care, Philadelphia, Lippincott-Raven, 1997.  
 Sprayberry KA: Hemorrhage and hemorrhagic shock. Bluegrass Equine and Critical Care Symposium Proceedings, 1999.

## CHAPTER 5.35

# Retained Fetal Membranes

CLAIRE CARD

*Saskatoon, Saskatchewan, Canada*

Passage of the fetal membranes represents the third stage of labor, and in normal healthy mares with uncomplicated deliveries is usually accomplished within 2 hours of foaling. Fetal membranes that are not delivered within 4 to 6 hours of foaling are generally considered to be retained. Retention of the fetal membranes (RFM) is the most common postpartum problem in mares. The incidence of RFM is low in the general population, involving less than 5% of foaling mares. Physical involution of the uterus in the healthy postpartum mare is an amazingly rapid process. Vanderplasse (see readings list) was the first author to report that uterine involution is so rapid that the uterus has already reduced to one and one half times its nonpregnant size within 12 hours of parturition. Any interruption or delay in uterine contractility because of alterations in the periparturient maternal or placental environment predisposes the mare to RFM. The fetal membranes and uterus are easily and quickly contaminated with bacteria. Debris and bacteria cause persistent uterine inflammation, and exudative endometritis. Exponential bacterial growth may overwhelm the mare's uterine defense mechanisms, resulting in endotoxemia and septicemia.

### ETIOLOGY, INCIDENCE, AND PATHOGENESIS

Risk factors for RFM in the mare include fescue, abortion, dystocia, placentitis, uterine inertia, twin pregnancy, premature parturition, and endophyte exposure. Iatrogenic retention may follow cesarean section if the chorioallantois is

inadvertently sewn into the uterine closure. Mares that have a previous history of RFM or that are identified as susceptible to persistent uterine inflammation and infection during the previous breeding season may be overrepresented in the group of mares presented for RFM. Many mares with RFM experience no adverse sequelae. Those mares with RFM that develop clinical illness and endotoxemia usually have gram-negative bacterial infections. Common gram-negative bacterial isolates include *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. Gram-negative infections of the postpartum uterus and placental tissues may arise from trauma, preexisting placentitis, contamination during dystocia, unsanitary examination, a contaminated foaling environment, or poor perineal conformation.

### DIAGNOSIS

The history may include the failure of all or part of the membranes to be delivered, but more often the fetal membranes are observed to be hanging out through the vulva. An evaluation of the fetal membranes may reveal that only a portion of the membranes has been delivered. The tip of the nonpregnant horn is the most common area of the placenta to be retained. However, inflammation from a preexisting placentitis may cause the placenta to adhere to the uterus, and thus the missing piece may come from any inflamed uterine location.

In early cases of RFM the physical examination findings may be in the normal range, or may include only slight elevations in body temperature and pulse. These mares of-



The additional expense of the following adjunctive medications may be deemed necessary once the mare has stabilized:

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In early cases of RFM the physical examination findings may be in the normal range, or may include only slight elevations in body temperature and pulse. These mares of-

ten do not show the typical postpartum cramping that accompanies placental delivery. Changes in body temperature may occur quickly, and thus body temperature alone is not a sensitive or reliable indicator of the status of the uterus and the presence of RFM. The longer the duration of RFM, the more likely the following clinical signs will be present: fever, endometritis, abnormal vaginal discharge, and uterine subinvolution. In advanced cases, endotoxemia may result from bacterial infection, and the clinical signs will include depression, laminitis, dehydration, inappetence, tachycardia, tachypnea, decreased milk production, decreased mothering ability, and toxic mucous membranes. The latter is indicated by bounding digital pulses, inflamed coronary bands and hooves, reluctance to walk, shifting weight, saw-horse stance, and even recumbency. Terminal cases of toxic metritis are septicemic, and progress into shock with disseminated intravascular coagulation, and eventual death.

Examination of the fetal membranes is described in Chapter 5.32. The following discussion concerns a missing piece of membrane. The examiner should be able to determine the *in situ* location of the pregnant and non-pregnant horn portions. The membranes should be positioned in the shape of the letter Y with the red velvety chorionic surface facing out. The body of the placenta forms the straight part of the Y, with the horns forming the arms of the Y. The examiner then inserts a gloved hand inside the chorioallantoic sac at the ruptured cervical star, and holds the membrane wide open to form a tent. A look inside allows a view of the insertion of the umbilical cord near the bifurcation of the horns on the allantoic surface of the placenta. If the umbilical cord runs toward the ventral surface then the membrane is positioned upside down. The examiner should turn it over and repeat the process of viewing the insertion of the cord. When the membranes are correctly positioned, the umbilical cord will attach onto the dorsal surface. The left and right sides of the fetal membranes now correspond to their *in situ* location in the uterus. When a piece of the membrane is missing, the examiner is now able to determine which horn contains the tissue remnant.

Vaginal examination may or may not show the RFM coming through the cervix. Small pieces of the fetal membranes may be retained within the uterus, and the amniotic membrane may break away and leave no evidence of RFM. In more advanced cases, especially where the membranes have been retained for more than 24 hours, a purulent vaginal discharge is often present. All postpartum mares have some normal uterine discharge (lochia); this discharge is moderately thick, nonodorous, and reddish brown in color. Postpartum mares may also pool urine. Fluid in the vagina should be examined to differentiate lochia, urine, and purulent matter.

Transrectal ultrasonography of the uterus complements the vaginal examination. Young healthy mares have little to no free intrauterine fluid the day following parturition. Ultrasonography allows the examiner to directly visualize the uterus and its contents, and it is one of the best means to determine if fluid is present in the uterus. However, the large size of a subinvolved uterus makes it difficult to visualize the entire organ during the examination. The examiner may see free-floating tags of RFM, or identify in-

tensely hyperechoic regions. Hyperechoic regions are not a normal finding in postpartum mares and indicate gas, debris, or trapped membranes. Serial ultrasonography of the uterus allows the character and depth of fluid to be measured and monitored.

Clinicopathologic features of RFM in early, uncomplicated cases are variable and usually mild. In more advanced cases the clinicopathologic changes are often severe and show evidence of dehydration, neutropenia, and leukopenia. A significant left shift with a band (2%-8%) neutrophilia, with toxic changes is usually present.

Daily monitoring of uterine involution by rectal examination, coupled with an evaluation of a complete blood count (CBC), is an excellent means of determining if the current therapy is efficacious. Resolution of uterine discharge, good uterine involution, and a normal CBC indicates that all of the RFM and debris have been removed. Persistent poor uterine tone and drainage along with a deteriorating leukogram suggests a poor response, and the therapeutic plan needs to be reevaluated. If the uterine problem appears to be resolved yet a degenerate left shift remains, the clinician should look elsewhere for a source of inflammation.

## TREATMENT

Although many mares with RFM do not become clinically ill, early prophylactic intervention is widely practiced because the complications associated with RFM may be severe and potentially life threatening. Many farm managers and horse owners with a veterinary client-patient relationship may be instructed to begin intramuscular (IM) injections of oxytocin 2 to 4 hours postpartum if the fetal membranes have not been passed. The membranes should be tied up above the hocks to prevent soiling and tearing. Tying a weight (e.g., a brick) to the membranes is not recommended because it may predispose the mare to development of a uterine horn intussusception. Injections of oxytocin should be given every hour for at least 6 treatments. The half-life of oxytocin in the mare is brief (12 min).

The initial starting dose of oxytocin should be on the low side (10-20 IU/500 kg) because sensitivity to oxytocin varies widely. The dose of oxytocin can then be tailored to each individual mare. A positive response will result in passage of uterine fluid from the vagina. Mares should be monitored following injection because any obvious cramping will begin within 10 minutes of IM injection. If a 10- to 20-IU oxytocin treatment does not result in an outward manifestation of discomfort by the mare, such as sweating and restlessness, then the dose can be increased in 10- to 20-IU increments until an effect is noticed. The dose should only be high enough to elicit mild colic signs. Mares with uterine inertia because of dystocia may be initially very resistant to the effect of oxytocin and may become more sensitive in the subsequent hours. If cramping and rolling result then the dose should be reduced. Some mares become inattentive mothers during the time when they are distracted by RFM or uncomfortable from the oxytocin-induced cramping. Thus the foal should be kept in a safe place when the mare is in pain. Nursing should be encouraged to stimulate the natural release of oxytocin associated with milk letdown.

If the mare fails to respond to six oxytocin injections or if she is clinically ill, a thorough veterinary examination is indicated. One option is to start an intravenous (IV) drip of oxytocin at 0.1 IU/ml of saline (i.e., 100 IU oxytocin per 1 L saline). The IV flow rate should be set so that the mare has visible signs of contractions every 5 to 10 minutes. The oxytocin drip treatment protocol will, in effect, revert the mare back into labor for about 1 hour.

The technique described by Burns and colleagues (1977; see readings list) works best when the membranes are fresh. Some clinicians perform the procedure prophylactically after a dystocia to reduce the likelihood of membrane retention. The clinician should wear waterproof clothing and a sterile surgical glove over a clean rectal sleeve. The perineum of the mare and external portion of the membranes are washed thoroughly. The opening at the cervical star, which leads into the allantoic cavity, is identified. A clean large-bore stomach tube is introduced, and the membranes are gathered around the tube. In addition, 4 L or more of a warm 1% povidone iodine solution is pumped or gravity fed into the chorioallantois until the fluid overflows. The tube is withdrawn as the RFM are tied shut with umbilical tape. Oxytocin may then be administered so that the uterus contracts against the distended membranes. This technique distends the endometrial crypts and often permits release of the microcotyledons. If the procedure is unsuccessful then it may be repeated several hours later. However, the retained membranes soon become autolytic and tend to tear as soon as distention starts.

If partial retention of the membranes is diagnosed, or if the membranes are badly torn, the uterus may be distended with 1% povidone iodine solution as described previously. The fluid distention and uterine contractions may help loosen the membranes. If the piece of membrane can be reached, it may be gently teased off the endometrium and removed. However, if the membrane tag is firmly adhered then continued traction is contraindicated. Once or twice daily flushing and the process of autolysis will eventually loosen the membranes. This procedure also may be carefully performed in mares that retain the membranes after a cesarean section. However, it is important to use a lower volume of infusate so that the uterine closure and fibrin seal are not disrupted.

Toxemic mares that are clinically ill and are passing a fetid uterine discharge may require systemic support with IV fluids, frequent IV treatments with oxytocin, and twice daily high-volume uterine lavage. Gentle manual removal of the fetid membranes may be necessary in these mares. Back and forth uterine lavage is performed with a clean stomach tube, bilge, or stomach pump. A dilute (1%) povidone iodine solution or sterile fluids are used to remove bacteria and inflammatory debris from the uterus. The clinician should hold the end of the tube cupped in the hand within the uterine cavity to prevent the tube from forcefully sucking against the wall when the fluid is being siphoned back. During the first few lavage procedures, persistence and patience in obtaining a clean return from the uterus is often rewarded with rapid clinical improvement and uterine involution. Lavage should be repeated once or twice daily until all debris is removed, the lavage is clear, and the uterus is well involuted.

Prophylactic administration of antibiotic and antiin-

flammatory medication is often prescribed early in the course of RFM in an attempt to prevent complications. Common antimicrobial choices are trimethoprim sulfa (30 mg/kg, q24h PO), or procaine penicillin G (22,000 IU/kg q12h IM) for a minimum of 3 to 5 days. If the mare is systemically ill then broad-spectrum medications such as penicillin-aminoglycoside combinations are recommended. The formulations or derivatives of penicillin include the following: procaine penicillin (22,000 IU/kg q12h IM), sodium and potassium penicillin (22,000 IU/kg q6h IV), ampicillin (50 mg/kg q8h IV), or ticarcillin (44 mg/kg q8h IM) for resistant cases. Aminoglycosides such as gentamicin (6 mg/kg q24h IM or IV) or amikacin (6.6 mg/kg q12h IV or IM) are used for mixed and gram-negative infections or resistant cases. Appropriate antibiotic use is confirmed by uterine culture and sensitivity results.

The mostly commonly used antiinflammatory medication for endotoxemic mares is flunixin meglumine, 1.1 mg/kg IV. In milder cases, flunixin meglumine (0.25-0.5 mg/kg q8h IV), ketoprofen (2 mg/kg q12h IV), vedaprofen (2 mg/kg q12h PO), or phenylbutazone (4 mg/kg IV or PO) are used. Hyperimmune plasma is administered if it is available.

Laminitis in mares with RFM is a serious complication. Lateral radiographs of the distal phalanx will help establish the degree of rotation, and the prognosis. Symptomatic care such as hosing the hooves with cold water, or application of foam pads or special shoes to the hooves can provide extra support and promote comfort. Phenylbutazone at 2 g every 24 hours by mouth is sometimes used prophylactically.

Mares with lactation failure should be treated with domperidone at 1.1 mg/kg orally every 12 hours to encourage lactation.

## PROGNOSIS

The prognosis for fertility is dependent on clinical progression of the condition. Mares with RFM may have normal fertility if no complications develop or if the treatment is prompt and the response is rapid. Mares with toxic conditions may experience a degree of fertility impairment, and should be monitored to ensure that uterine involution is complete before breeding.

## Supplemental Readings

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## CHAPTER 5.36

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# Perineal and Cervical Lacerations

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Three natural barriers protect the uterus from bacterial contamination. The cervix, vulvar lips, and vestibular sphincter are all susceptible to trauma during foaling, and especially during obstetrical manipulations. Serious life-threatening complications, however, seldom result from these injuries.

### PERINEAL LACERATIONS

Perineal lacerations occur during unassisted foaling, most commonly in primiparous mares. Lacerations are caused by a combination of foal limb malpositioning and the violent, unpredictable expulsive efforts that accompany equine parturition. The foal's hooves can engage the roof of the vestibule during forceful contractions and may lacerate the dorsal wall of the vestibule. The resulting injury is classified as either a first, second, or third-degree perineal laceration, or a rectovestibular fistula. First-degree lacerations involve only the vestibular mucosa and vulvar skin at the dorsal commissure. Second-degree lacerations involve the vulvar mucosa, submucosa, and perineal body musculature. Third-degree lacerations result from the foal's foot perforating the rectum and tearing all the structures between the rectum and vestibule caudally to include the dorsal vestibular wall, rectum, perineal body, and anal sphincter. Third-degree lacerations result in a common opening between the rectum and vestibule. Rectovestibular fistulas result from the foal's foot perforating the rectum but then withdrawing the foot before subsequent normal delivery. The result is a fistula of variable size between the rectum and vestibule, usually cranial to the perineal body. The external genitalia in these cases will appear normal.

Diagnosis of these conditions is made during the postpartum examination, although third-degree perineal lacerations will be immediately obvious to the owner and may cause serious alarm (Figure 5.36-1). Injury to the perineal body, anal sphincter, and dorsal vulvar commissure are readily apparent on visual inspection. Even with less severe injuries, external examination of the perineum will usually reveal edema, bruising, stretching, and splitting of the vulvar skin and mucosa. Speculum and manual examination are necessary to determine the degree of injury to the vestibule and vagina. Rectal palpation will confirm the presence of a rectovestibular fistula. Although other periparturient injuries may simultaneously occur, no reported associations exist with the occurrence of perineal lacerations. Thus no reason exists to be unduly concerned about the potential for other foaling-related injuries that may not be detected on a routine postpartum examination.

Classification of the type of laceration on the basis of the involved structures is useful because it will accurately predict the required treatment. First-degree lacerations will heal uneventfully with no surgical intervention other than possibly a Caslick's procedure. Second-degree lacerations frequently will heal completely without intervention because the tissues are maintained in apposition. Damage to the perineal body or vestibular musculature that does not completely heal can be repaired at a later date. Third-degree lacerations and rectovestibular fistulas will always require surgical repair. However, immediate surgery is ill advised regardless of the type of injury. In the acute phase the wounds are extremely edematous, contaminated with feces, and some tissues may not be viable. Repair must be delayed at least 4 to 6 weeks until complete healing has occurred before reconstruction of the damaged perineum is attempted. During this interval, any devitalized tissue will slough and second intention healing will occur. Fibroplasia will take place and remodeling of the deposited fibrous tissue provides greater holding power for sutures. Complete epithelial resurfacing occurs so that visual examination of the laceration will reveal a line of junction where the rectal mucosa meets the vestibular mucosa (Figure 5.36-2). Reconstructive surgery may be performed at any time after complete healing has occurred. Surgery performed 6 to 8 weeks postfoaling is optimal; however, other management concerns such as weaning of the foal or getting the mare in foal for next year often factor into the timing of the surgical repair. It is advisable to forewarn owners contemplating surgical repair that more than one attempt is often required to achieve reconstruction.

### Treatment

Immediate treatment should be directed at medical management to minimize discomfort, prevent infection, and promote wound healing. Tetanus prophylaxis is indicated according to the recommended guidelines. Pain and inflammation secondary to trauma should be treated with phenylbutazone (4.4 mg/kg PO q24h). The wounds are invariably severely contaminated and thus benefit from broad-spectrum antimicrobial treatment. Antimicrobial therapy may be discontinued in 7 to 10 days once a healthy bed of granulation tissue is present. Affected mares may experience difficulty in defecation as a result of perineal discomfort, and impaction can be a secondary complication. The feces can be kept soft by initial prophylactic administration of mineral oil through a nasogastric tube, and then with subsequent doses administered in the feed. Mares on lush green pasture may not require assistance to achieve



**Figure 5.36-1** Third-degree perineal laceration approximately 1 week postfoaling. Note the edema, fecal contamination, and the absence of mucosa.



**Figure 5.36-2** Completely healed third-degree perineal laceration approximately 2 months postfoaling that is ready for surgical repair.

fecal softening. Local wound care involves providing as clean an environment as possible. Manual evacuation of feces from the vestibule is beneficial in the early stages of healing for third-degree lacerations and rectovestibular fistulas. Gross fecal contamination of the vagina and uterus is seldom a concern because the injuries invariably occur caudal to the vestibular sphincter. Daily, or twice daily, lavage of the wound with antibacterial solutions such as dilute povidone iodine (10 ml of 10% stock solution/L of water) is beneficial for the first few days. The practitioner should resist the urge to aggressively surgically debride the lacerated tissues. Surgical repair depends on reconstruction of the shelf between the rectum and the vestibule. Retention of as much viable tissue as possible will improve the chances for

successful surgical reconstruction. Tissue that is clearly nonviable should be promptly removed; however, the trauma and associated inflammation may make it difficult to differentiate between viable and nonviable tissues. This difficulty can easily result in removal of viable tissues. It is preferable to take a more conservative approach and to debride the laceration over several days, each time removing only the definitively nonviable tissue.

Mares with first- or second-degree lacerations seldom require surgery. Third-degree lacerations and fistulas result in chronic, low-grade bacterial contamination of the vagina and uterus; therefore surgical repair will be required for breeding soundness. Uterine contamination and subsequent endometrial degeneration secondary to these injuries has been documented by culture and biopsy. Any inflammatory uterine changes are reversible after surgical repair. Studies have shown that 75% of mares are able to successfully carry a foal after surgical repair of third-degree perineal lacerations or rectovestibular fistulas. Mares that have undergone surgical repair are predisposed to reinjury on subsequent foalings; however, clinical experience indicates that the incidence of recurrence is low.

## CERVICAL LACERATIONS

Although cervical lacerations are most commonly associated with dystocia, they can occur during unassisted deliveries. The most common cause is a large fetus. Overzealous foaling attendants can increase the prevalence of cervical tears on a farm by applying traction to the fetal limbs before the cervix has fully dilated. Any assisted delivery should heighten awareness of the possibility of a cervical injury. Diagnosis at the time of fetal extraction is difficult because the cervix is edematous and widely dilated. Dilation of the cervical musculature results in a thin, flaccid cervix that is not readily identifiable on speculum or digital examination during the immediate postpartum period. Inability to confirm the presence of cervical tears at the time of injury is not an impediment since surgical repair should not be attempted until complete uterine involution has occurred. The acutely damaged cervical tissue will be edematous and friable. The recently gravid uterus will be heavy, and difficult to retract caudally to permit surgical accessibility. Some healing of the lacerated cervix will occur spontaneously and no medical therapy other than routine postpartum care is required.

Confirmation of a cervical tear is made during a reproductive exam approximately 30 days postfoaling. Manual examination of the cervix is required because the outline of the cervical os during speculum examination may appear normal if the mucosa is intact. This is frequently the case. Digital examination is accomplished by a combination of the thumb and index finger. Typically the clinician inserts the index finger into the cervical canal and palpates the thumb against it circumferentially around the cervix. The goal is to detect any defect of the cervical musculature as evidenced by thinning of the cervical wall. The optimal time to perform this examination is during diestrus. Progesterone supplementation can be used for 2 to 3 days before the examination to ensure maximal cervical closure. The external cervical os should provide an initial level of resistance to the forward progression of the

index finger. The location of lacerations is usually reported in reference to the face of a clock, and the length is reported in centimeters. The length of the defect must be estimated because some tears may not warrant repair. Defects that involve only a small percentage of the length of the cervical canal may still provide a functional barrier to the gravid uterus. Cervical defects that involve less than 25% of the length of the cervix probably do not require surgical intervention. Defects involving between 25% to 50% of the length of the cervix may benefit from repair. Defects of 50% or greater do require repair if the mare is to have a chance of carrying a foal to term. Obviously surgical repair is only indicated if the mare is to be used for breeding. The prognosis for future fertility following sur-

gical repair of a lacerated cervix is reported to be approximately 60%. Owners should be advised that the cervix is unlikely to dilate normally after surgical repair, and that it is likely to tear again. Close monitoring of mammary secretions (electrolyte changes) can be used to select the most optimum time for an elective cesarean section.

### ***Supplemental Readings***

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# SECTION VI

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## Hematopoietic Diseases

*Edited by Dr. Michelle Henry Barton*

### CHAPTER 6.1

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## Diagnostic Approach to Anemia

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**A**nemia, defined as an absolute reduction in the circulating red blood cell (RBC) mass, is a frequently encountered clinical problem in the horse. Differences in the rate of onset and degree of anemia, coupled with variety in etiology, present a diagnostic challenge. Furthermore, unique features of the physiologic response to anemia in the horse do not lend to accurate classification of the anemia on the basis of regeneration, unless a bone marrow aspirate is obtained. With this in mind, it often is helpful to use the clinical signs, physical findings, and basic laboratory tests to initially classify the anemia on the basis of cause—such as blood loss, increased RBC destruction, or anemia of inadequate erythropoiesis—to further pursue a specific etiologic diagnosis. If this approach is unavailing, a bone marrow aspirate can be performed to determine whether the anemia is regenerative (i.e., caused by blood loss or increased RBC destruction) or nonregenerative due to inadequate erythropoiesis.

### CLINICAL SIGNS AND PHYSICAL FINDINGS

The underlying etiology, rate of development, and extent of reduction of RBC mass determine the clinical signs. Whether acute or chronic, significant anemia is accompanied by pallor of the mucous membranes and lack of visible episcleral blood vessels. Decreased blood viscosity may lead to turbulent blood flow in the heart and result in a low-grade systolic murmur typically audible with greatest intensity over the semilunar valves. The main physiologic response to anemia directly reflects the degree of impairment in the oxygen-carrying capacity of the blood. Thus with chronic anemia of gradual onset, signs often are subclinical. However, the compensatory response to chronic anemia often is overwhelmed by the challenge of exercise, whereupon weakness, reduced performance, or sudden collapse may occur. In contrast, the physiologic response to acute anemia is manifested by immediate attempts to increase oxygen delivery to the vital organs and is charac-

terized by tachycardia, tachypnea, and peripheral vasoconstriction. When these physiologic adaptations are insufficient, weakness, collapse, blindness, ataxia, dementia, colic from ileus, laminitis, or oliguria may ensue as oxygen deprivation to the respective tissues progresses. Acute increase in metabolic demand on the cardiovascular and hematopoietic systems may cause a low-grade fever, especially typical of hemolytic and blood loss anemias.

### Blood Loss

Additional clinical signs or physical findings may provide clues into the etiology. Signs of hypovolemic shock frequently accompany acute, severe blood loss. Evidence of external blood loss may be obvious, such as the presence of epistaxis, melena, hematochezia, hematuria, or trauma. Signs of internal hemorrhage often are less obvious. Intrathoracic hemorrhage may cause tachypnea, shallow rapid breathing, and dyspnea. Acute intraabdominal hemorrhage may cause ileus, colic, or abdominal distention. Coagulopathy as a cause of blood loss may be manifested clinically as frank or occult bleeding, petechial or ecchymotic hemorrhages, or prolonged bleeding following minor invasive procedures or trauma. Because bleeding results in loss of both red blood cells and protein, symmetric dependent edema may be an important clinical clue of hypoproteinemia.

### Hemolysis

Icterus is an important clinical feature of increased RBC destruction (hemolysis) when the total bilirubin concentration exceeds 3 mg/dl. Icterus must be carefully evaluated in horses, as it also is a clinical feature of anorexia and liver disease. Furthermore, because the presence of icterus depends on the rate and extent of RBC destruction in relation to hepatic clearance of bilirubin, lack of icterus does not preclude a diagnosis of hemolysis. Nonetheless, intense icterus in the horse is usually the result of hemolysis—more

typically intravascular than extravascular. Signs of hypovolemia may accompany acute hemolysis. Hemoglobinuria is often the first important clinical clue of intravascular hemolysis but will not occur unless the renal threshold for hemoglobin is exceeded. Both intravascular and extravascular hemolysis result in icterus of the sclerae, whereas the reduction in RBCs causes a lack of episcleral vessels. Icterus of mucous membranes may overshadow the pallor of anemia.

### Inadequate Erythropoiesis

The clinical signs of nonregenerative anemia are more obscure because of the slow onset of development, the well-established compensatory responses, and the fact that anemia in this category is usually secondary to a chronic underlying primary disease. Pallor of the mucous membranes, lack of episcleral vessels, lethargy, or exercise intolerance are typical. Icterus and edema are not features, unless they are associated with the underlying primary disease.

## DIAGNOSIS OF ANEMIA

### General

The diagnosis of anemia is confirmed by the laboratory demonstration of reductions in the packed cell volume (PCV), hematocrit (HCT), hemoglobin concentration, and RBC count. A reduction in these indices that is not associated with clinical signs warrants reassessment. Several conditions may complicate accurate determination of the red cell count and indices and should be considered in evaluation of the erythron. The PCV and RBC count vary with age, breed, or use of the horse. For example, the PCV of neonates less than 2 days of age is similar to that of the adult. However, the PCV of foals decreases rapidly in the first week of life, and erythrocytes are normochromic to hypochromic, normocytic to hypochromic. The PCV typically remains below normal adult values until approximately 18 months of age. In general, well-conditioned or "hot-blooded" horses, such as the Thoroughbred have a greater PCV (32%-53%) than poorly conditioned, "cold-blooded" draft breeds or Miniature Horses (24%-44%). Finally, dehydration and splenic contraction may conceal anemia and should be taken into account when evaluating the erythron.

RBC morphology may provide some clues to the cause of the anemia. Heinz bodies, precipitates of hemoglobin that are best seen with New Methylene blue stain, indicate oxidative injury. Spherocytes and schizocytes indicate immune-mediated anemia and disseminated intravascular coagulopathy, respectively. Small nuclear remnants called *Howell Jolly bodies* may normally be present in small numbers in the circulation of horses. Rouleaux, or a "stacking" appearance to the peripheral RBCs, is normally extensive in horses.

Once anemia is confirmed by an absolute decrease in the RBC count, an etiologic diagnosis is needed to guide therapy and prognosis. Although history, clinical signs, or physical findings may be sufficient for accurate etiologic diagnosis, additional testing is often needed (Table 6.1-1). One classic pathophysiologic scheme for categorizing ane-

mia depends on determination of whether regeneration is evident. A regenerative anemia is one in which the bone marrow responds appropriately to the RBC reduction by increasing RBC production in the bone marrow with subsequent release into the circulation. Blood loss anemia and hemolysis are types of regenerative anemias. A feature unique to the horse is the fact that their erythrocytes remain in the bone marrow until fully mature, even in the face of severe anemia and intense erythropoiesis. Therefore peripheral evidence of erythrocyte regeneration typically found in other species—such as reticulocytosis, macrocytosis, anisocytosis, polychromasia, Howell-Jolly bodies, basophilic stippling, and nucleated RBCs—is rarely found in the horse.

Because of the lack of obvious evidence of regeneration in the peripheral blood of the horse, the RBC indices are not highly useful for classification of anemia. However, a mild to moderate increase in the mean corpuscular volume (MCV) and anisocytosis are the most common hints of regeneration in the horse. These latter changes are more likely to occur with hemolytic anemia rather than with blood loss and usually do not occur until 2 weeks after the onset of anemia. An increased mean corpuscular hemoglobin (MCH) or mean corpuscular hemoglobin concentration (MCHC) indicates the presence of free hemoglobin subsequent to either *in vitro* or *in vivo* hemolysis. Microcytic, hypochromic, and macrocytic states are seldom observed in the horse, although moderate to severe iron deficiency may cause microcytic, hypochromic anemia. The RBC volume distribution width, an indicator of variation of the RBC volume that may be provided by some automated blood cell counters, increases with regeneration. Increases in RBC creatine and glucose-6-phosphate dehydrogenase concentrations may correlate with increased MCV and immature RBCs in the circulation in horses. The most reliable measure of the bone marrow's responsiveness to anemia in horses requires evaluation of a bone marrow aspirate (see the following discussion). The diagnosis of blood loss or hemolytic anemia typically can be made without bone marrow evaluation.

### Blood Loss Anemia

The diagnostic approach and differential diagnosis for blood loss anemia are detailed in Chapter 6.2. In general, anemia accompanied by hypoproteinemia without intense icterus would be expected with blood loss anemia (see Table 6.1-1). Splenic contraction and redistribution of fluid may obscure full assessment of the degree of anemia for 24 to 48 hours after acute bleeding. Furthermore, intact RBCs and protein can be reabsorbed to some extent after internal bleeding. Although blood loss anemia is not typically accompanied by icterus, extensive internal bleeding may cause mild to moderate icterus as the extravasated RBCs are phagocytized. Because iron is available for reuse, the bone marrow response to internal blood loss tends to be more rapid than it is to external loss, whereas loss of iron with extensive external blood loss may rarely result in nonresponsive iron deficiency anemia. Mature neutrophilia is a nonspecific finding that commonly accompanies intense regenerative anemia.



**Table 6.1-1**  
**Diagnostic Approach to Anemia**

Cause	Findings
<b>Regenerative Anemia</b>	
<i>Blood loss anemia</i>	Mucous membrane pallor with or without edema Lack of episcleral vessels Hypoproteinemia Possible mild icterus
1. Internal	No icterus
2. External	Chronic form may be accompanied by iron deficiency
<i>Hemolysis</i>	Mucous membrane pallor Icterus (rule out liver disease and anorexia) No edema Lack of episcleral vessels Normal to increased total protein
1. Intravascular	Intense icterus Hemoglobinemia/uria Increased free Hgb, MCH, and MCHC Urine dipstick blood positive
2. Extravascular	Icterus without hemoglobinemia/uria Normal free Hgb, MCH, and MCHC Urine negative for blood
<b>Nonregenerative Anemia</b>	
<i>Anemia of chronic disease</i>	Mucous membrane pallor without edema or icterus Normal to increased serum protein Rule out other causes Anemia mild to moderate and normocytic normochromic Serum iron and total iron binding capacity normal to decreased Normal to increased serum ferritin Increased iron stores in bone marrow
<i>Other</i>	Microcytic, hypochromic anemia with increased serum iron, serum ferritin, and increased total iron binding capacity with iron deficiency Bone marrow aspirate demonstrating erythroid hypoplasia in association with aplastic anemia or myelophthisis

*Hgb*, Hemoglobin; *MCH*, mean corpuscular hemoglobin; *MCHC*, mean corpuscular hemoglobin concentration.

### Hemolytic Anemia

Concurrent anemia and hyperbilirubinemia without hypoproteinemia characterize hemolysis (see Table 6.1-1). Exclusion of other causes of hyperbilirubinemia, such as anorexia and liver disease, is helpful in “ruling in” hemolytic disease. Typically, hyperbilirubinemia characterized by increased unconjugated bilirubin is most intense with intravascular hemolysis.

Acute intravascular hemolysis causes hemoglobinemia that is easily verified by grossly examining the color of the plasma. Low-grade intravascular hemolysis may be insufficient to grossly discolor the plasma red but may be detected by an increase in the MCH or MCHC. If the renal threshold for hemoglobin is exceeded, hemoglobinuria—detected either as grossly red to red-brown urine or subclinically as a positive blood reading on routine “dipstick” analysis—may be additional evidence of intravascular hemolysis. Caution should be exercised when interpreting a “positive” blood test on urine dipstick analysis as it de-

fects free hemoglobin, intact RBCs, and myoglobin. Ammonium sulfate saturation test on the urine will distinguish hemoglobin from myoglobin. Because hemoglobin is rapidly cleared from the plasma and converted to unconjugated bilirubin, icterus following intravascular hemolysis typically develops within 24 hours of onset of hemolysis. Mature neutrophilia is a nonspecific finding that commonly accompanies intravascular hemolysis.

Diagnostic evidence of extravascular hemolysis is more difficult to definitely determine. An episode of intravascular hemolysis in which sufficient time has passed to allow for clearance of hemoglobin from the plasma and urine could be confused with extravascular hemolysis. The presence of hyperbilirubinemia and anemia—without hypoproteinemia—or evidence of liver disease or intravascular hemolysis would be presumptive evidence of extravascular hemolysis. Differential diagnoses for both intravascular and extravascular hemolysis are discussed in more detail in Chapter 6.4.

### Inadequate Erythropoiesis

Anemia due to inadequate erythropoiesis occurs when the rate of RBC maturation is inadequate to replace the normal loss of aging RBCs from the circulation. Because the problem lies within the blood marrow, this type of anemia is called *nonregenerative*. It generally develops slowly and reflects the 5-month equine RBC lifespan. Plasma protein concentration varies but often increases with chronic inflammation or neoplasia (see Table 6.1-1). Hyperbilirubinemia is not expected unless the underlying disease process is hepatic or causes significant anorexia. Diagnosis of anemia of inadequate erythropoiesis is by exclusion of blood loss or hemolytic anemia and may require evaluation of a bone marrow aspirate to be definitive. The majority of anemias in this category are due to anemia of chronic disease and will resolve if or when the underlying disease is resolved. The anemia is generally mild to moderate. Thorough and systematic physical and laboratory evaluation is needed to determine the underlying cause. Differential diagnoses for anemia of inadequate erythropoiesis are discussed in Chapter 6.3.

### Bone Marrow Aspirate

In horses, bone marrow may be collected from the sternum, rib, or ileum; however, the sternal site is generally preferred. The sternal skin on the ventral midline between or slightly behind the olecranons is clipped and aseptically prepared. A subcutaneous block with 2% lidocaine and/or sedation may facilitate patient compliance. A stab incision through the skin with a number-15 blade may be necessary when using large biopsy needles. A 3.5-inch 18-gauge spinal needle with stylet in place or a core biopsy needle may be used. Use of a spinal needle seems to be well tolerated and is quicker. The needle is briskly inserted through the skin—perpendicular to the flat sternal plate, on the midline in the cleavage between the pectoral muscle—and advanced until the tip reaches bone. At this point, the needle should be rotated back and forth until it is firmly embedded into bone. The stylet then is removed and a 20-ml syringe attached. The syringe plunger should be pulled gently to the 10-ml mark and released while the needle is stabilized in the bone. This maneuver should be

repeated two to three times. If marrow or blood is seen in the hub of the needle, suction should be released immediately to prevent blood from diluting the marrow aspirate. If marrow or blood is not obtained, reintroduce the stylet, advance the needle, and repeat the aspiration. Smears should be made immediately after collection and air-dried. Aspiration of bone marrow from the sternum is generally easy, quick, well tolerated, and without complication. Rare reports have documented the needle slipping into the thoracic cavity and nicking the heart. Proper patient restraint and/or ultrasound-guided aspirates should reduce this risk. Bone marrow core biopsies can be collected with a Jamshidi infant marrow biopsy needle with the same procedure as is used for collecting aspirates. Once the needle is inserted, the stylet is removed, and the needle is rotated unidirectionally. No aspiration is applied. The core biopsy is removed from the needle by inserting the stylet into the beveled end of the needle to push the core out the hub. The core may be rolled onto a slide for an impression smear but then should be inserted into 10% formalin fixative for histopathology.

The normal myeloid to erythroid ratio (M:E) in horses ranges from 0.5 to 2.4 and is best evaluated by a clinical pathologist or someone with considerable experience in examining bone marrow aspirates. M:E ratios of less than 0.5 and the presence of at least 5% reticulocytes are generally consistent with an appropriate bone marrow response to anemia in the horse. The maturity of the erythroid compartment should also be assessed. In normal horses, 70% to 90% of erythroid cells are rubricytes and metarubricytes. Prussian blue stain can be used to assist in the evaluation of bone marrow iron stores.

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## CHAPTER 6.2

# Blood Loss Anemia

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### ACUTE BLOOD LOSS

The pathophysiologic effects of acute blood loss result from decreased circulating blood volume and associated hypovolemic shock. Hemorrhage becomes clinically significant when over 30% of the body's blood is lost rapidly. Because blood volume represents approximately 8% of body weight, this loss constitutes 10.8 liters in a 450-kg horse. Unfortunately, accurate quantification of blood loss is rarely possible; thus assessment of the presence and severity of hemorrhage is based on clinical signs and sequential measurement of packed cell volume (PCV) and plasma protein.

Severe hemorrhage usually is due to loss of vascular integrity, which may result from iatrogenic (surgery) or accidental trauma or from erosion of vessel walls by neoplastic, infectious, or parasitic lesions. Rarely, coagulopathies such as an inherited or acquired factor deficiency, thrombocytopenia, or disseminated intravascular coagulopathy cause clinically significant acute blood loss. Common causes of external hemorrhage caused by large vessel rupture include castration complication or accidental trauma. Epistaxis associated with nasal surgery or guttural pouch mycosis also can result in severe blood loss. Rarely, exercise-induced pulmonary hemorrhage, ethmoid hematoma, or nasal neoplasia cause serious epistaxis. Internal hemorrhage occurs most often into large muscle masses, the abdominal cavity, or the thorax. In muscle, jagged fracture fragments or severe soft-tissue trauma can lacerate large vessels. Traumatic splenic rupture or spontaneous middle uterine artery hemorrhage in postpartum mares can cause hemoperitoneum. Less often, mesenteric vessels may be damaged by large strongyle migration, mesenteric abscessation, or neoplasia. Similar erosive processes, such as a pulmonary abscess or neoplasia, as well as trauma, can cause hemothorax.

### Clinical Signs and Diagnosis

Consistent signs include tachycardia, tachypnea, pale mucous membranes, and prolonged jugular filling. With continued bleeding, progressive exercise intolerance, muscular weakness, and collapse ensue. Decreased organ perfusion can cause oliguria and ileus. With internal hemorrhage, signs associated with the site of blood accumulation may be present. These include dyspnea and pleurodynia in cases of hemothorax, low-grade colic associated with hemoperitoneum, or lameness due to hemarthrosis or muscle hemorrhage.

The source of massive extracorporeal bleeding usually is obvious. However, internal or multifocal bleeding may re-

quire a careful physical examination to discern clinical signs of hemorrhage and to differentiate them from other signs of abdominal, thoracic, or musculoskeletal disease. When a typically nonhemorrhagic emergency—such as colic, pleuritis, or acute musculoskeletal trauma—is encountered, internal bleeding should always be considered if tachycardia, tachypnea, and mucous membrane blanching persist after the patient is stabilized. Auscultation, percussion, centesis, and percutaneous ultrasonography are useful ancillary diagnostic aids. If no source of vascular damage to account for the hemorrhage can be identified, then the diagnostic work-up should include a platelet count and clotting profile that includes prothrombin time, activated partial thromboplastin time, and fibrin degradation products.

In the first 12 to 24 hours after acute hemorrhage, the severity of blood loss must be estimated on the basis of clinical signs, unless the actual volume of hemorrhage has been quantified. This estimation is necessary because several physiologic alterations render the PCV and plasma protein unreliable indicators of bleeding. First, increased sympathetic nervous system activity triggers splenic contraction, thus releasing stored red blood cells that temporarily support the PCV. Concurrently, decreased hydrostatic pressure within capillaries causes interstitial fluid to move into the vascular space. This begins within 30 minutes of acute hemorrhage and can restore 20% to 50% of blood volume within 6 hours. Subsequently, further translocation of interstitial fluid, absorption of fluid from the gastrointestinal tract, and renal water resorption all act to support intravascular volume but dilute the PCV. Thus the PCV continues to decrease until the true severity of blood loss can be assessed in 24 to 36 hours after hemorrhage ceases. Plasma protein is reclaimed from lymph during fluid shifts after bleeding. As a result, plasma protein, which is a more useful indicator of severity of hemorrhage in the first hours after bleeding, increases more rapidly than PCV thereafter. In cases of internal hemorrhage, the interpretation of PCV and plasma protein is further complicated by the recycling of up to two thirds of the erythrocytes and most of the protein lost into extravascular spaces within the body. The bone marrow response to hemorrhage is not reflected by any increase in PCV until 3 to 5 days after the hemorrhage, and normal red blood cell mass may not be restored for 4 to 6 weeks. In general, the clinicopathologic indicators of response to hemorrhage seen in other species are not present in horses. Leukocytosis and thrombocytosis are rare. Occasionally, the mean corpuscular volume (MCV) will increase above 60 fl by 4 to 7 days after hemorrhage.

## Treatment

The two immediate goals of treatment for acute blood loss are: (1) to stop the bleeding and (2) to reverse hypovolemic shock. External hemorrhage is best controlled with direct pressure or large vessel ligation. With internal hemorrhage, physical and environmental stress are minimized. Surgical intervention to identify and control sites of internal hemorrhage usually is not practical. Although the reports are anecdotal, the anti-fibrinolytic agents epsilon-aminocaproic acid (Amicar; 5 grams IV) and tranexamic acid (Cyklokapron; 1 gram IV) as well as the narcotic antagonist naloxone hydrochloride (Narcan; 8 mg IV) have been used without deleterious effects to treat postpartum uterine artery hemorrhage. Aminocaproic and tranexamic acid directly inhibit the fibrinolytic action of plasminogen. In humans, these drugs decrease intracranial hemorrhage, bleeding after cardiopulmonary bypass, and dysfunctional uterine bleeding. Naloxone apparently combats the effects of endogenous opioids on cardiovascular dynamics. Equivocal results have been reported in experimental studies that investigated the efficacy of naloxone in the treatment of hypovolemic shock. The efficacy of neither the antifibrinolytic agents nor naloxone has been evaluated objectively in horses. Finally, anecdotal claims to the efficacy of intravenous administration of 0.37% formaldehyde to treat uncontrolled hemorrhage have been reported. Unfortunately, objective evaluation of seven healthy horses that were administered 0.37% and 0.74% formaldehyde showed no effect on CBC, serum biochemical analyses, template bleeding time, or activated clotting time. In addition, higher doses resulted in adverse effects including muscle fasciculations, tachycardia, tachypnea, agitation, and restlessness.

If clinical signs of hypovolemic shock are present, an intravenous crystalloid solution should be administered rapidly at 40 to 60 ml/kg to provide cardiovascular support. Other potential fluid choices include hypertonic saline and colloid solutions. The use of hypertonic saline in the face of uncontrolled hemorrhage is controversial because some experimental evidence demonstrated increased blood loss and mortality caused by the increased blood pressure and cardiac output that follow hypertonic saline administration. If bleeding has been stopped, 7% saline at 4 ml/kg IV (2 L to a 450-kg horse) may be beneficial, particularly if high-volume crystalloid solution administration is not practical in a field setting. Following the hypertonic saline with appropriate isotonic fluids within two hours is important. Although colloid solutions such as dextran, hydroxyethyl starch, or plasma often are cost-prohibitive or unavailable, the use of hydroxyethyl starch solutions (Hespan) to treat hypovolemic shock in equine practice is increasing. When administered intravenously at 8 to 10 ml/kg, 6% hydroxyethyl starch produced a significant positive oncotic effect for 24 hours in 11 hypoproteinemic horses. The use of hydroxyethyl starch as a resuscitative fluid in the face of acute blood loss should be reserved to cases in which bleeding has been controlled, because a dose-dependent decrease in prothrombin time, activated partial thromboplastin time, and fibrinogen concentrations is associated with its administration.

After stabilization, the necessity for whole blood transfusion must be assessed. With acute blood loss, if blood

pressure and circulatory volume are adequate, myocardial oxygenation is maintained until the hematocrit falls below 15%. The decision for transfusion is based on the overall clinical assessment of the patient. (See Chapter 6.7 ["Blood and Blood Component Therapy"] for specific recommendations regarding transfusion.)

## CHRONIC BLOOD LOSS

Chronic blood loss is uncommon in the horse but, when present, is most often secondary to gastrointestinal parasite infestation. Other sources of gastrointestinal blood loss include infiltrative diseases such as gastric squamous cell carcinoma or ulcers secondary to nonsteroidal antiinflammatory drug toxicity. Urogenital bleeding secondary to neoplasia or infection is possible, and idiopathic urethral hemorrhage in male horses has been reported. Thrombocytopenia or coagulopathy should always be considered when chronic blood loss is suspected.

## Clinical Signs and Diagnosis

Overt clinical signs of anemia are not associated with gradual loss of red cell mass until the PCV falls below 12%. Subtle signs such as lethargy and pale mucous membranes may be noted earlier, as may clinical signs related to the underlying disease—such as weight loss in the case of parasitism or neoplasia. The primary rule-outs for anemia due to chronic blood loss are anemia of chronic disease and low-grade hemolysis.

Diagnostic work-up is aimed at characterizing the anemia, identifying a source of blood loss, and ruling out other causes of anemia. Therefore complete blood count, bone marrow evaluation, fecal occult blood, fecal examination for parasite ova, urinalysis, total and indirect serum bilirubin, and a Coggins test for equine infectious anemia all are indicated. Chronic blood loss should result in a regenerative anemia; however, peripheral signs of erythrocyte regeneration are inconsistent in the horse and at best include an increase in mean corpuscular volume and mild anisocytosis. Bone marrow evaluation with a myeloid/erythroid ratio of less than 0.5 indicates a regenerative response.

Although iron deficiency anemia is rare in horses because dietary iron usually is abundant, circulating erythrocytes account for over 65% of the body's iron stores. Depletion of iron stores by chronic bleeding can be confirmed by the presence of hypoferremia, increased total iron binding capacity, decreased marrow iron, and a poor regenerative marrow response. The associated nonregenerative anemia typically is microcytic, hypochromic.

## Treatment

Treatment is based on identification and elimination of the source of blood loss. Because patients with chronic anemia have often had sufficient time to adjust physiologically, transfusion is rarely needed. If evidence of decreased iron stores exists, ferrous sulfate can be supplemented orally at 2 mg/kg daily. Administration of parenteral iron is not recommended because of the possibility of serious adverse reactions.

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## CHAPTER 6.3

# Anemia Secondary to Inadequate Erythropoiesis

CHRYSANN COLLATOS

*Reno, Nevada*

The average lifespan of the equine erythrocyte is 150 days. Therefore anemia caused by inadequate erythropoiesis is an insidious process associated with scant, nonspecific clinical signs. Causes include anemia of chronic disease, nutritional deficiency, bone marrow aplasia, or myelophthistic disease. Of these, anemia of chronic disease (ACD) associated with infectious, inflammatory, or neoplastic disorders is most commonly encountered in horses.

### ANEMIA OF CHRONIC DISEASE

ACD is well-recognized in mammalian species. Three mechanisms have been incriminated in the disease process: shortened erythrocyte life span, insufficient bone marrow response to demand for red blood cells, and decreased release of iron from the reticuloendothelial system.

Accelerated red cell destruction may be the result of activation of the mononuclear phagocyte system in response to inflammation. Also, the intravascular response to inflammation may cause increased erythrocyte damage during passage through small vessels with subsequent removal by the reticuloendothelial system. Normally, the bone marrow would respond to such increased consumption with an appropriate increase in red blood cell production. The rate-limiting factor in the marrow's failure to respond to anemia of chronic disease may be inadequate erythropoietin production. Erythropoietin is the hormone primarily responsible for regulation of erythropoiesis in the bone marrow. Although erythropoietin production is increased in people and in animal models of anemia of chronic disease, the hormone is deficient relative to the anemia. Administration of pharmacologic doses of recombinant erythropoietin will reverse ACD. In addition to the relative erythropoietin deficiency, erythroid progenitor cell activity is inhibited in ACD, as is iron release from the reticuloendothelial system. It appears likely that the abnormal bone marrow and iron me-

tabolism responses in ACD are mediated by cytokines produced in response to inflammatory conditions, including infection and neoplasia. Interleukin-1, tumor necrosis factor, and  $\gamma$ -interferon all have been shown experimentally to play roles in ACD.

### Diagnosis, Clinical Signs, and Treatment

ACD is diagnosed by the presence of a chronic disease process accompanied by a mild to moderate, nonregenerative, normochromic, and normocytic anemia. Serum iron and total iron-binding capacity are decreased, but normal to increased iron stores can be demonstrated by normal serum ferritin concentration or positive Prussian blue stain for marrow iron.

The clinical signs of anemia of chronic disease are those related to the primary disease, and treatment is solely related to eliminating the underlying disease condition and to ensuring that the anemia is not caused by blood loss or hemolysis. Diseases associated with anemia of chronic disease in horses include pleuropneumonia, internal abscessation, peritonitis, chronic organ failure, immune-mediated or granulomatous diseases, neoplasia, and chronic viral disease such as equine infectious anemia. Although hypoferremic, horses with ACD have normal iron stores and do not require iron supplementation.

### NUTRITIONAL DEFICIENCY

Inadequate erythropoiesis caused by dietary inadequacy is rare in horses. Vitamin B<sub>12</sub> and folic acid are important cofactors in erythrocyte maturation. In horses, gastrointestinal bacteria synthesize vitamin B<sub>12</sub>, thus eliminating the need for exogenous consumption. Absorption deficiency, as seen in pernicious anemia in people, is not recognized. Deficiencies in other micronutrients involved in erythrocyte production—such as copper, cobalt, and iron—are rare. Iron-deficiency anemia in horses is almost invariably

### Supplemental Readings

Jones PA, Bain FT, Byars TD et al: Effect of hydroxyethyl starch infusion on colloid oncotic pressure in hypoproteinemic horses. *J Am Vet Med Assoc* 2001; 208:1130-1135.

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the result of chronic blood loss. Iron-deficiency anemia is diagnosed on the basis of hypoferritinemia, hypoferrremia, normal to increased total iron binding capacity, and detection of decreased iron stores on examination of bone marrow aspirate. In horses, normal serum ferritin has been reported as  $152 \pm 54.6$  ng/ml, normal iron concentration as  $120 \pm 5.0$   $\mu$ g/dl, and normal total iron binding capacity as  $388 \pm 8.1$   $\mu$ g/dl.

Iron metabolism changes rapidly in foals. Serum iron concentration is very high in the first few days of life; under no circumstances should oral or parenteral iron supplementation be given during this period. Thereafter, some controversy regarding the presence of a functional iron deficient state in the first 4 to 6 weeks of life exists because of the high iron demands associated with rapid growth and a milk diet that is relatively poor in iron. Recently, iron deficiency was reported in a group of stabled Dutch warmblood foals that were housed indoors and fed freshly cut grass. These foals were listless compared to control foals on pasture. In addition, stabled foals had significantly lower hemoglobin concentrations, packed cell volumes, blood iron concentrations, and saturation total iron binding capacities. Laboratory values and attitude scores improved in stabled foals after oral iron supplementation.

### ANEMIA DUE TO BONE MARROW APLASIA OR MYELOPHTHISIS

Aplastic anemia results from congenital or acquired developmental failure of hematopoietic progenitor cells in the bone marrow. In other species, acquired aplastic anemia has been associated with bacterial and viral infections, chronic renal or hepatic failure, irradiation therapy, and drug administration, but the majority of cases are considered idiopathic. Until recently, aplastic anemia had only been reported in a few horses. No definitive cause was identified, although one horse had a positive Coombs test, thus suggesting an immune-mediated process. Phenylbutazone was implicated in two other cases. In the 1990s the advent of unapproved administration of a human recombinant erythropoietin to racehorses resulted in the emergence of a drug-induced immune-mediated anemia characterized by potentially fatal bone marrow erythroid suppression.

Endogenous erythropoietin, produced by the liver and activated in the kidney, stimulates red blood cell production by the bone marrow, thereby regulating maintenance of a normal peripheral red blood cell count. In an attempt to enhance performance by increasing circulating red cell mass, recombinant human erythropoietin (Epogen) has been administered to healthy racehorses. The recombinant product induces the production of antierythropoietin antibodies that cross-react with the horse's endogenous erythropoietin. Endogenous erythropoietin thus is inactivated, and bone marrow red cell production is depressed. Complete shutdown of red cell production that results in fatal aplastic anemia has been reported in horses that were administered repeated doses of human recom-

binant erythropoietin. Local racing commissions should be contacted concerning any suspected case.

### Clinical Signs, Diagnosis, and Treatment

Horses with advanced anemia caused by bone marrow hypoplasia show nonspecific clinical signs such as poor performance and weight loss as well as pale mucous membranes. Definitive diagnosis of aplastic anemia is based on bone marrow assessment. In two horses with erythroid hypoplasia and anemia after administration of recombinant human erythropoietin, bone marrow myeloid/erythroid ratios were 6.7 and 3.2 (normal 0.5-1.5), thus indicating severe, nonregenerative anemia. These horses also had increased serum iron concentrations, normal total iron binding capacities, and increased serum ferritin concentrations. Recombinant human erythropoietin can be detected in the plasma of horses for only 72 hours after dosing. Use of recombinant human erythropoietin can be suspected in horses if anti-EPO antibodies are detected in the patient's serum or if endogenous erythropoietin levels are abnormally low (EPO Trac RIA, Incstar, Stillwater, Minn.).

In addition to aplastic anemia, pancellular bone marrow destruction secondary to neoplastic infiltration or myelofibrosis has been reported in the horse. In such cases, clinical signs are associated with loss of the shorter-lived cells, neutrophils, and platelets. Therefore fever, localized infection, and thrombocytopenic hemorrhage can be anticipated.

Treatment of aplastic anemia is focused on identification of underlying cause and on corticosteroid administration. Steroids stimulate erythropoiesis by increasing erythropoietin production and the sensitivity of stem cells to this hormone's action. One horse with idiopathic aplastic anemia improved after administration of nandrolone decanoate (Deca-Durabolin), an anabolic steroid, and corticosteroids, and two horses with human recombinant erythropoietin-induced anemia recovered after drug withdrawal and administration of corticosteroids.

No successful treatment currently is available for myelophthitic diseases associated with pancytopenia.

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## CHAPTER 6.4

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# Hemolytic Anemia

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**H**emolytic anemia is a pathologic condition that results from accelerated erythrocyte removal and can be intravascular and extravascular. Intravascular hemolysis occurs when erythrocytes are destroyed within the vascular space. Clinical signs associated with intravascular hemolysis are typically acute in onset and classically include icterus and red- to port-wine-colored urine. Extravascular hemolysis results from accelerated erythrocyte removal by macrophages in the spleen or liver and is characterized by icterus without hemoglobinuria.

### DISEASES THAT PRIMARILY CAUSE INTRAVASCULAR HEMOLYSIS

#### Oxidative Erythrocyte Damage

Oxidant damage to erythrocytes can develop following exposure to a variety of oxidizing agents such as phenothiazines, onions, or wilted red maple (*Acer rubrum*) leaves. The latter cause is by far the most common. The oxidizing agent causes hemoglobin to become denatured with subsequent disulfide bond formation. Oxidized hemoglobin forms precipitates referred to as Heinz bodies that are visible with Romanowsky's-stained blood smears. These cell changes result in increased fragility of cells with subsequent intravascular hemolysis and enhanced removal by the mononuclear phagocytic system in the spleen and liver. In addition, oxidative damage causes increased permeability of the membrane, thereby altering ion transport mechanisms and osmotic gradients. Due to these changes, erythrocytes may rupture within the vascular lumen, thus resulting in intravascular hemolysis and microangiopathy. In contrast to oxidative damage that leads to erythrocyte destruction, altered oxygen carrying capacity results when hemoglobin is oxidized and forms methemoglobin. Methemoglobinemia occurs when more than 1.77% of the hemoglobin is oxidized from the ferrous ( $\text{Fe}^{2+}$ ) to the ferric ( $\text{Fe}^{3+}$ ) state by oxidizing agents.

Because *A. rubrum* is a common tree in the eastern United States, toxicity associated with red maple leaf ingestion is a fairly common clinical disease in that region. Although the specific toxic agent in the plant has not been identified, a seasonal trend appears to exist for the development of disease because more cases are associated with ingestion of wilted or dried leaves in the fall than for leaves ingested in the spring.

#### Clinical Signs and Diagnosis

In cases of red maple toxicity, a combination of intravascular and extravascular hemolysis develops over a variable

period of 2 to 6 days. In severe cases, clinical signs of hemolytic anemia and tissue hypoxia secondary to methemoglobinemia may develop more rapidly. The prognosis for horses suffering from red maple toxicity is guarded; the approximate survival rate is 60% to 70%. Clinical signs result from the combined effects of tissue hypoxia and hemolysis that results in fever, tachycardia, tachypnea, lethargy, intense icterus, and hemoglobinuria, with characteristic brown coloration of skin, mucous membranes, and—if methemoglobinemia is present—blood. Hematologic abnormalities include anemia, increased mean corpuscular hemoglobin concentration and mean corpuscular hemoglobin, free plasma hemoglobin, anisocytosis, poikilocytosis, eccentrocytes, lysed erythrocytes that produce fragments or membrane ghosts, agglutination, increased RBC fragility, variable presence of Heinz bodies, and neutrophilia. Serum chemistry abnormalities include increased total and indirect bilirubin, serum creatinine, and serum urea nitrogen concentrations, reduced RBC glutathione and increased aspartate aminotransferase, sorbitol dehydrogenase, creatinine phosphokinase, and gamma-glutamyl transpeptidase activities.

Additional abnormalities may include hypercalcemia and hyperglycemia, with a variable degree of metabolic acidosis. Urinalysis findings could include any combination of the following: hemoglobinuria, methemoglobinuria, proteinuria, bilirubinuria, and urobilinogenuria. Methemoglobin can be quantified spectrophotometrically. Red maple leaf, wild onion, or phenothiazine toxicosis would be strongly suspected if a history of exposure or opportunity for exposure exists. Diagnosis is based on clinical signs of an acute onset primarily of intravascular hemolytic crisis supported by laboratory evidence of oxidative damage—that is, Heinz bodies or methemoglobinemia. Additional differential diagnoses for methemoglobinemia should include familial methemoglobinemia and nitrate toxicity, both of which are exceptionally rare in the horse.

#### Treatment

Treatment for oxidative injury involves reducing the fragility of erythrocytes, maximizing tissue oxygenation, maintaining renal perfusion, and providing supportive care. The horse needs to be removed from the environmental source of the toxin and treated with activated charcoal (8–24 mg/kg up to 2.2 kg PO) via nasogastric tube to reduce further absorption of red maple toxin. Dexamethasone (0.05–0.1 mg/kg IV q12–24h) may be helpful to stabilize cellular membranes and reduce extravascular removal of erythrocytes by phagocytes. Ascorbic acid



(10–20 g PO q24h) is often used to maintain cellular  $\alpha$ -tocopherol in the reduced form and as a scavenger of free radicals. No data support the use of methylene blue as a reducing agent in horses; in fact, it may exacerbate oxidative damage. Oxygen insufflation may be required for horses that suffer from severe hypoxia. Whole blood transfusion from a compatible donor should be considered in those horses that demonstrate severe hemolytic disease. These signs include a severe reduction in venous oxygen tension ( $PVO_2$ ) and increased anion gap or packed cell volume (PCV) 10% to 12% with evidence of cardiovascular and respiratory distress. In cases of severe hemolysis, pigmentary nephropathy—induced by the combination of excess filtration of hemoglobulin and hypoxemia—may be a complication. Renal function should therefore be monitored during the course of treatment. Intravenous fluids are administered as needed, but hemodilution in anemic patients should be avoided. If acute renal failure develops, diuretic agents such as dopamine, furosemide, or mannitol may be indicated. In high-risk patients, drug therapy should be designed to avoid additional potentially nephrotoxic agents such as aminoglycosides and non-steroidal antiinflammatory drug (NSAID) agents.

### Prognosis

Complications are a major component of morbidity following severe hemolysis. Poor tissue oxygenation may lead to cerebral anoxia and altered mentation, renal failure, and myocarditis. Blood transfusion may result in colic secondary to reperfusion of hypoperfused bowel. Laminitis is always a concern in horses with severe illness and may be compounded by the use of corticosteroids. Disseminated intravascular coagulopathy may develop secondary to severe hemolysis.

In conclusion, horses should not be housed in areas with access to red maple trees or other potential oxidants. Good quality forage should be available at all times to reduce the likelihood of horses ingesting leaves as they fall or blow into pastures. Other maple varieties of trees should be considered potentially dangerous; reports have suggested clinical signs consistent with red maple toxicity when affected animals were exposed to red maple hybrids.

### Additional Causes of Intravascular Hemolysis

Microangiopathic hemolysis may be associated with vessel thrombosis. Hemolysis is secondary to intravascular fibrin accumulation and may be characterized by the presence of schizocytes. This is a potential complication that is characteristic of chronic disseminated intravascular coagulation (DIC) in horses. Fulminant liver failure also carries the potential complication of hemolysis. Clinical evidence is consistent with intravascular hemolysis that includes icterus and hemoglobinuria. The severity of hemolysis contributes to mortality in most cases. Lesions at necropsy are consistent with DIC. It has been proposed that alterations in exchangeable RBC lipoprotein are affected by increased bile acids, thus contributing to altered metabolism of red cells resulting in hemolysis.

Toxin exposure may result in acute intravascular hemolysis. Snakebites that result in envenomation with potential hemolysis include: rattlesnakes (*Crotalus* spp.),

pigmy rattlesnakes (*Sistrurus* spp.), copperhead (*Agkistrodon* spp.), cottonmouth (*Agkistrodon piscivorus*), or water moccasins. Snake toxins comprise more than 90% proteins that include proteolytic and phospholipase enzymes. These toxins are well known to induce episodes of severe hemolysis and altered coagulation mechanisms. Bacterial exotoxins produced from *Clostridium* spp. and some staphylococcal pathogens carry the potential of inducing severe intravascular hemolysis, which is especially apparent in septic neonatal foals. Although rare in horses, infection by *Leptospira pomona* and *Leptospira icterohaemorrhagiae* serotypes have been reported to cause acute intravascular hemolysis in several large animal species. Intravenous iatrogenic administration of hypotonic fluids or undiluted dimethyl sulfoxide (DMSO) or excessive administration of water enemas to neonates may result in hemolysis. Although rare, heavy metal intoxication may also cause hemolysis.

## DISEASES THAT PRIMARILY CAUSE EXTRAVASCULAR HEMOLYSIS

### Neonatal Isoerythrolysis

The primary differential diagnosis for a neonatal foal observed to have evidence of anemia and intense icterus during the first week of life is neonatal isoerythrolysis (NI). Incompatible blood group antigens between the mare and stallion combined with maternal exposure to fetal erythrocytes during gestation results in maternal production of antigen specific antibodies targeted against the foal's red blood cells, if the foal inherited the sire's red blood cell phenotype. The most common blood types associated with NI in foals are Aa and Qa. Foals with NI most commonly suffer from extravascular hemolysis, although rare intravascular hemolysis occurs concurrently. A positive direct Coombs' test provides a presumptive diagnosis of NI. However, the most sensitive diagnostic technique for identification of surface-associated immunoglobulin (Ig) molecules on suspect foal red blood cells involves a new direct immunofluorescence (DIF) assay using flow cytometry. In this assay, isotype specific antibodies bind to red blood cells that contain surface-associated antibodies, thus providing a quantitative measure of erythrocytes in the circulation that are bound with antibody. Chapter 12.2 provides more information on the pathophysiology and treatment of NI.

### Immune-Mediated Hemolytic Anemia

Immune-mediated hemolytic anemia (IMHA) results from cross-reacting antibodies that induce enhanced red blood cell removal. Autoimmune (primary IMHA) hemolysis results from loss of self-tolerance and is relatively rare in horses. Most commonly, hemolysis results from adherence of cross-reacting antibodies to erythrocyte surface antigens (secondary IMHA). The presence of these molecules on red blood cells causes intravascular destruction by complement activation (IgM-mediated) or—most commonly—extravascular removal by macrophages. It is important for the reader to consider that any infectious agent—especially equine infectious anemia, *Babesia* organisms, and *Anaplasma phagocytophila*; exogenous substances such as

penicillin and phenylbutazone; or neoplasia—may cause alterations in epitopes of the erythrocyte membrane or *neoantigens* that contribute to enhanced removal by immune mechanisms. Therefore identification of the inciting cause is important for complete resolution of the hemolytic crisis.

Several possibilities may explain the onset of cellular destruction. The basic mechanisms involve a change in the red blood cell or an alteration in immunologic control of self-recognition. For example, a change in the red blood cell membrane may form a novel antigen that evokes an immune response. Drugs, neoplasia, or infection may induce changes in red cell antigens. Infectious agents that express similar antigens as host red blood cell antigens result in pathogen-induced immune-mediated hemolysis, termed *molecular mimicry*. An example of molecular mimicry is human infection with Epstein-Barr virus. Genetic predispositions may cause a failure of self-tolerance. Failure of autoregulation has been suggested to result from reduced suppressor lymphocyte control. Finally, failure of appropriate erythropoiesis may result from precursor erythrocytes being targeted by the immune response in a manner similar to that of circulating red blood cells. The goal of the clinician should be to focus on identifying any potential inciting causes because this will allow for appropriate case management with the best prognosis for efficient and complete disease resolution.

#### **Clinical Signs and Diagnosis**

Horses with IMHA most commonly present with signs of extravascular hemolysis, but intravascular hemolysis is possible, especially when IgM antibodies or complement is involved. Spherocytes may be present on cytology of peripheral blood smears. Diagnosis based on autoagglutination will suggest surface-bound antibody. Dilution of the sample with saline (1:1) will indicate whether true agglutination is present. If erythrocytes still agglutinate after dilution, they can be considered positive for surface-bound antibody molecules. Tests that are used for the diagnosis when autoagglutination is absent are the direct and indirect Coombs' test; the direct test is more sensitive. The Coombs' reagent is polyclonal sera directed against equine IgG, IgM, IgA, and C3 and is used in serial dilutions. The endpoint of the Coombs' test is agglutination, but it can also be used to test for antibody- or complement-mediated lysis. Direct Coombs' test may yield a false-negative result if an incomplete set of reagents is used, if blood is not tested at both 4° C and 37° C, or if severe hemolysis has resulted in removal of the majority of antibody-coated RBCs from circulation. As previously described, a new direct immunofluorescence assay that uses class-specific antibodies to equine IgM, IgG, and IgA and flow cytometry has an increased sensitivity to detect red cell antibodies for the diagnosis of IMHA.

#### **Treatment**

Therapy will be determined based on the level of anemia. In severe cases, whole blood transfusion may be indicated. Specific guidelines are given under Blood and Blood Component Therapy (see Chapter 6.7: "Blood and Blood Component Therapy"). Current drug administration should be

discontinued. If, based on confirmed sepsis, antimicrobial therapy is required, drug therapy should be continued with a molecularly dissimilar drug. After blood samples for diagnostic tests (i.e., Coombs' test or direct immunofluorescence assay) are obtained, immunosuppressive therapy may be considered. Most affected horses require immunosuppression with corticosteroids. Because immunosuppression carries the risk of potentiating infectious agents, underlying infectious disease conditions such as equine infectious anemia should be ruled out. Glucocorticoid therapy benefits the patient in the short term by reducing the function of macrophages to recognize antibodies complexed to red blood cells and in the long term by altering antibody production by B-lymphocytes. Dexamethasone used at 0.05 to 0.2 mg/kg IV q24h has been reported to have the greatest efficacy in treating IMHA in horses. The PCV should be monitored carefully during the course of steroid therapy, and if the patient does not respond quickly, the frequency of administration may be increased to twice daily. In some instances, it may take up to a week for the full effect of steroid therapy to be reflected by a rise in PCV. Once the PCV is stable at greater than 20%, the steroid therapy should be carefully tapered by 0.01 mg/kg/day, while the horse is closely monitored for recurrence of hemolytic crisis. The major adverse reactions to long-term administration of corticosteroid in horses are laminitis, tendon laxity or weakness, and immunosuppression that leads to secondary infections. Therefore the goal is to reduce to the lowest effective dose as soon as possible. Alternate day therapy should be administered for the last week of therapy. Some individuals may require therapy for several weeks until disease resolution occurs. Although only a single equine case report has been published, the use of azathioprine (5 mg/kg PO q24h) and cyclophosphamide (300 mg/m<sup>2</sup> body surface area) was successful in managing a case of refractory IMHA.

#### **Equine Infectious Anemia**

Equine infectious anemia (EIA) is a retroviral disease characterized by chronic episodic pyrexia and hemolytic anemia. No apparent breed or gender predilection exists, but it is reported most commonly in the southeastern United States. The acute form of the disease has a course of fever, depression, and thrombocytopenia that is clinically represented by mucosal petechiation. Horses infected for more than 30 days have the subacute to chronic form of the disease and show anorexia, ventral edema, and episodic fever spikes. Occasionally, horses may have abdominal pain, ataxia, abortion, or infertility induced by inflammation of the affected organ system. Although not common, deaths may be observed during the subacute to chronic phases of disease. Many horses recover from the initial phases of the disease, but episodic flare-ups will continue throughout the first year of infection. Persistence of virus in the face of detection of an antibody response indicates reduced immune clearance. Therefore it is logical to assume that immune suppression can occur during times of environmental stress and thus can lead to recrudescence of disease. In some individuals, clinical signs of disease are not apparent, and diagnosis is incidentally made on annual serologic testing. This population of

horses represents a carrier state and is a significant threat to uninfected horses.

Hematologic evidence of disease includes thrombocytopenia during the acute phase of disease with anemia and icterus developing during the subacute to chronic phases of disease. Additional changes may include leukopenia with lymphocytosis and monocytosis. During episodes of hemolysis, increased serum antibody-coated erythrocytes may be detected. Hyperglobulinemia, increased serum liver enzyme activities, and proteinuria may develop during the chronic stages of disease.

### **Pathogenesis**

Equine infectious anemia results from infection with a high molecular weight-enveloped RNA retrovirus that contains RNA-directed DNA polymerase. This molecular machinery gives the virus the ability to incorporate into host genome of infected macrophages. Although horses produce a substantial humoral immune response, viral elimination does not occur, and affected horses remain infected for life.

Transmission of the virus occurs through the transfer of blood between infected and uninfected horses, thus resulting in persistence of disease. Although blood is commonly implicated, some authors question whether other body secretions may contribute to viral spread. The most common route of infection is through the interrupted feeding of hematophagous arthropods such as horseflies (*Tabanus* spp.) and deerflies (*Chrysops* organisms). The level of viremia is greatest during episodes of fever and anemia, and this is the time in which disease transmission is most efficient. Iatrogenic transmission may occur through the use of blood-contaminated instruments, and the potential for transplacental transfer can occur in approximately 10% of viremic mares. The virus is tropic for macrophages and acts like the "Trojan horse," providing latency. After viral replication the viral particles are released from the macrophage into the surrounding extracellular milieu, thus introducing a cycle of viral amplification within the host. Serologic detection of disease is best performed after 16 to 42 days of infection. Due to continued immune responsiveness that results from periodic cycles of viral replication, hyperplasia of the lymphoreticular system and hypergammaglobulinemia develop in chronically infected horses.

Hemolysis is considered to result from immune complex attachment to RBCs via a viral hemagglutinin, with subsequent extravascular removal of cells by the mononuclear phagocytic system. Additional mechanisms for virus-induced anemia involve reduced bone marrow erythrocyte production through induction of suppressive cytokines. Episodic flare-ups of EIA are believed to result from antigenic drift of the virus with stimulation of cycles of immune responses.

### **Diagnosis, Management, and Prevention**

The preferred diagnostic test for EIA is the Coggins test, which is an agar gel immunodiffusion assay. An alternative test is the enzyme-linked immunosorbent assay (ELISA). The Coggins test has the advantage of good sensitivity for chronically infected horses, whereas the ELISA has fast turn-around time but lower specificity. Early in

the course of disease the humoral response may be low, and false-negative test results can occur with the Coggins test. A small percentage of chronically infected horses may test negative. Alternatively, passive transfer of colostral antibodies in foals may result in false-positive results. Repeat testing in both cases will indicate the true incidence of disease in the host. These examples support the suggestion made by many authors that repeat evaluation of EIA status is recommended at a minimum of a 30-day interval before introduction into a herd.

Horses found to be positive for EIA must be reported to state and federal agencies. Testing is required for national or international transport, either with the Coggins test or the ELISA. In general, boarding facilities and show and race agencies as well as other competitions require evidence of EIA-negative status for all participants. No treatment is available for viral clearance in positively infected horses. These animals remain a constant threat for viral infection to other horses; euthanasia is generally recommended. Chronically infected horses are in most cases in poor condition and unable to remain athletic. However, some horses remain subclinically affected and, although they pose a potential threat to other horses, they are able to maintain a good quality of life. In such cases or when valuable breeding animals are maintained, veterinarians must adhere to specific precautions. Absolute attention to restriction of blood transfer or blood-related material is crucial. Additional control measures include isolation of no less than 200 yards from any other horses and double screening in a stable environment. These precautions must be approved by the governing agencies of the specific location; different states have specific laws regarding these specifications.

### **Piroplasmosis**

Piroplasmosis is a tick borne disease of horses resulting from infection with one of two protozoan hemoparasites of the Apicomplexa subphylum *Babesia caballi* or *Theileria equi* (formerly *Babesia equi*). These are the only recognized intraerythrocytic diseases of horses. Natural transmission of disease is a result of tick infestation. Piroplasmosis is most commonly reported to occur in tropical or subtropical regions, although it is reported to occur rarely in temperate regions, which reflects the habitat of the natural tick vectors. *Babesia caballi* is transmitted transovarially from one tick generation to the next. *Theileria equi* is transmitted horizontally by species of *Dermacentor*, *Hyalomma*, and *Rhipicephalus*, which are rarely vectors for *B. caballi*. The primary vector is *Dermacentor nitens* that exists in regions where the temperature remains above 60° F. All horses can be infected with these parasites, but disease tends to be more severe in elderly horses. The history of infected horses often includes a recent episode of transport to an endemic region.

### **Clinical Signs and Pathogenesis**

Clinical signs are apparent in the first 1 to 4 weeks of infection and include fever depression, anorexia, weakness, ataxia, lacrimation, mucoid nasal discharge, chemosis, icterus, hemoglobinuria, and potentially death. Fatalities may occur within 48 hours of infection, but chronic dis-

ease often develops. Inapparent carrier horses that lack clinical signs are commonly found in endemic regions. Hematology may reveal parasitized RBCs early in the course of disease.

*B. caballi* or *T. equi* are the two species that infect horses, although only *B. caballi* has been reported in the United States—in Florida and Texas. Both species have been observed in the Americas, Europe, Asia, Africa, Middle East, and Russia. *B. caballi* organisms divide by binary fission, resulting in a pair of two organisms approximately  $3 \times 2$   $\mu\text{m}$  in length. *T. equi* measures approximately 1 to 2  $\mu\text{m}$  and is observed as an ovoid structure, located in groups of 4 that form a “maltese cross.”

*Babesia* and *Theileria* organisms infect and multiply within red blood cells. The majority of these infected cells are removed by the mononuclear phagocytic system, but some severely affected animals will suffer from intravascular hemolysis. Clinical disease induced by *T. equi* is more severe than that induced by *B. caballi* and has a higher mortality rate. Untreated horses will remain persistently infected for an undetermined period of time. Factors such as transport, inclement weather, pregnancy, or concomitant disease will have the potential for induction of clinical disease in carrier animals.

#### Diagnosis and Treatment

Diagnosis may be based on observation of parasitized erythrocytes with Giemsa-stained blood smears, isolation of the organism from the blood, or positive serology. Parasitemia precedes hemolysis so diagnosis is most commonly based on serology. *Babesia*- or *Theileria*-specific antibodies will be produced approximately 14 days after infection and can be determined with the complement fixation test or indirect fluorescent antibody test. Animals imported into negative regions must have a negative complement fixation test before entering the United States, Canada, Japan, or Australia. A PCR test that has greater sensitivity for detection of positive horses has been developed, but this test is not required to meet transport restrictions at this time.

Treatment is most successful with administration of imidocarb dipropionate to reduce the parasite load. Clearance of *B. caballi* is achieved with two doses of 2.2 mg/kg intramuscularly, administered 24 hours apart, whereas *T. equi* is more difficult to clear and requires four to six doses of 4 mg/kg intramuscularly, administered 72 hours apart. In some cases, *B. caballi* will spontaneously resolve. Reported efficacy is approximately 60%, especially in eastern Europe. Because of the anticholinesterase properties of the drug, patients should be carefully monitored for colic, hypersalivation, diarrhea, or—potentially—death. Donkeys have an increased sensitivity to imidocarb and should be treated at the lower dose (2.2 mg/kg IM q24h  $\times$  2 doses) and receive close monitoring of clinical signs.

#### Equine Ehrlichiosis

Equine ehrlichiosis is caused by the rickettsial organism *A. phagocytophila* (formerly known as *Ehrlichia equi*), which

belongs to the phagocytophilia complex of ehrlichial agents. *A. phagocytophila*, is the causative agent of tick-borne fever of ruminants that reside in Europe and human granulocytic ehrlichiosis (HGE) in Europe and America. This organism has DNA sequence homology with *A. phagocytophila* recovered from horses in Connecticut and California and HGE. Blood from people with HGE given to horses induces disease and imparts protective immunity to future challenge with *A. phagocytophila*. Equine ehrlichiosis is most common in the northern California foothills; however, ehrlichiosis has been reported in other regions of the United States, including the upper Midwest and the northeastern United States.

#### Clinical Signs and Diagnosis

Clinical signs include fever, depression, petechiae, ventral edema, and ataxia, with reluctance to move. Differential diagnoses for these signs include purpura hemorrhagica, equine viral arteritis, and encephalitis. Granulocytopenia, anemia, and thrombocytopenia are common abnormalities detected on hematology. Horses that are younger than 3 years of age exhibit a less severe form of the disease. Diagnosis of *A. phagocytophila* may be made from identification of morula in circulating granulocytes. Seroconversion (fourfold rise in serum antibodies in a convalescent sample) can be detected with an indirect fluorescent antibody test. A polymerase chain reaction assay has been developed for *A. phagocytophila* and has improved sensitivity and specificity in comparison to conventional diagnostic tests.

Supportive care for affected patients should include NSAID therapy, intravenous fluids, and lower limb sweat wraps. Intravenous oxytetracycline (7 mg/kg diluted in 1 liter of saline IV q24h  $\times$  5-7 days) is effective for clearance of equine granulocytic ehrlichiosis. Response to therapy is extremely rapid, thus supporting the diagnosis in suspect cases. Carrier phases have not been recognized; in fact, once-infected horses acquire strong immunity for up to 2 years, thus providing resistance to reinfection.

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## CHAPTER 6.5

# Thrombocytopenia

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### PATHOPHYSIOLOGY

Thrombocytopenia may result from a variety of inciting factors, but in general three major mechanisms are considered: (1) reduced platelet production, (2) abnormal platelet distribution (sequestration), or (3) increased consumption or decreased platelet survival. Thrombocytopenia causes altered hemostasis due to insufficient phospholipid substrate for coagulation proteins. The platelet plug localizes activated clotting factors and maintains vascular integrity, thus preventing spontaneous hemorrhage from developing. Although severe thrombocytopenia causes prolonged bleeding times, it will not affect clotting times or plasma fibrinogen concentration.

#### Reduced Platelet Production

Reduced platelet production may result from bone marrow aplasia or marrow infiltration due to neoplasia or severe inflammation. Myelophthisis (see Chapter 6.9: "Lymphoproliferative and Myeloproliferative Disorders") is an acquired process wherein the functional unit of marrow is destroyed and overtaken by a pathologic process. In such a case, pancytopenia will result and is a very uncommon outcome for equine patients. Intermittent thrombocytopenia with moderate to profound neutropenia was reported in 8 young Standardbred horses sired by the same stallion. Familial megakaryocytic and myeloid hypoplasia due to a bone marrow microenvironment or growth factor defect was suspected.

#### Increased Platelet Consumption or Destruction

Causes of increased platelet consumption and increased platelet destruction are most commonly disseminated intravascular coagulation (DIC; see Chapter 6.6: "Hemostatic Disorders") and immune-mediated thrombocytopenia (IMTP), respectively. IMTP is classified as either primary (idiopathic or autoimmune) or secondary—induced by drug administration, infection, or neoplasia. The most common infectious disorders associated with thrombocytopenia are equine infectious anemia and *Anaplasma phagocytophila*; however, chronic inflammatory disease of a variety of etiologies has been described to contribute to the development of thrombocytopenia. Neoplasms that contribute to thrombocytopenia most commonly are either lymphoma or hemangiosarcoma.

Alloimmune thrombocytopenia of neonates is an acquired disease that has been characterized in humans, pigs,

and horse and mule foals. Clinical signs in foals include depression, reduced affinity for the mare, tendency for hemorrhage, and potentially, blood loss anemia. Multiparous mares' Ig binds to foal platelets after passive colostral transfer. Alloimmune thrombocytopenia should be considered in neonatal foals that have evidence of severe thrombocytopenia when sepsis is ruled out and platelet antibody tests are positive. Platelet destruction in IMTP results from surface-associated antiplatelet antibody molecules. Primary IMTP results from antibody directed against platelet membrane antigens with complement-fixing Ig molecules. Rapid platelet removal will ensue because these antibodies target cells for immediate destruction and removal by macrophages in the spleen. Secondary IMTP results from Ig molecules binding to platelet Fc receptors. These antibodies are part of an immune complex that is targeted against a drug or infectious agent with binding to the platelet surface resulting in phagocytic removal. Antibody production associated with immune-mediated hemolytic anemia may also contribute to platelet destruction. Platelet lifespan is directly correlated to the level of immune complex coating on the platelet surface. Several hypothesized mechanisms for autoantibody production have been proposed and include suppressor T lymphocyte dysfunction, enhanced self reactive T lymphocytes, abnormal response mechanisms of B lymphocytes to T lymphocyte regulation, or stimulation of autoreactive B lymphocyte clones as a result of infection or inflammation.

### CLINICAL SIGNS AND DIAGNOSIS

Clinical signs of thrombocytopenia include hemorrhagic diathesis caused by small vessel bleeding and represented by petechiation, although ecchymosis of the ocular, oral, nasal, or vaginal mucous membranes may be observed. Epistaxis, hyphema, microscopic hematuria, or spontaneous hemorrhage may develop when the platelet concentration falls below 10,000/ $\mu$ l. Prolonged postoperative bleeding or hematomas at injection sites may become apparent with the concentration falls below 40,000/ $\mu$ l. Thrombocytopenia in combination with anemia is called Evan's syndrome and is most commonly associated with primary neoplasia or abscessation. Horses with primary idiopathic IMTP in which no underlying cause is found are often bright, alert, and normothermic and may not have spontaneous hemorrhage.

Diagnosis of thrombocytopenia depends on confirmation of a decreased platelet count ( $<100,000/\mu$ l). Pseudothrombocytopenia has been recognized in horses, as in

other species, as a consequence of platelet interaction with ethylenediaminetetraacetic acid (EDTA) anticoagulant. The process is believed to be a function of a blood protein related to fibrinogen that is maximally active at low calcium concentrations and reduced temperature. Pseudothrombocytopenia should be suspected when platelet clumping is reported or the mean platelet volume (MPV) is increased when EDTA is used as the anticoagulant. A 3.8% sodium citrate anticoagulated sample should be analyzed for more accurate platelet counts.

When abnormal PT, APTT, and fibrin degradation products (FDP) concentration accompany thrombocytopenia, DIC should be suspected. When a normal PT, APTT, plasma fibrinogen and FDP accompany thrombocytopenia, bone marrow disease or IMTP should be suspected. Bone marrow evaluation will identify megakaryocytic hypoplasia in the rare cases of decreased platelet production, whereas megakaryocytic hyperplasia is typical of increased peripheral consumption or destruction. Rarely, antibody has been identified against megakaryocytes and would cause ineffective production or release. The diagnosis of IMTP will be supported by the identification of surface-associated Ig molecules on peripheral platelets using direct immunofluorescence (DIF) and flow cytometry. Additionally, platelet regeneration in response to increased consumption or destruction can be suspected by an increase in the mean platelet volume or evaluated by staining peripheral platelets with the vital dye thiazole orange, which will bind to RNA present in immature platelets and can be detected with flow cytometry. In all cases of IMTP, ruling out or identifying potential underlying disease that may be triggering secondary IMTP, such as EIA or lymphoma, is important.

## TREATMENT

No treatment for primary bone marrow megakaryocyte hypoplasia exists. (Treatment for DIC is discussed in Chapter 6.6: "Hemostatic Disorders.") Treatment for IMTP is similar to immune-mediated hemolytic anemia. Medication withdrawal should be implemented with adjustment of antibiotic or drug therapy to a molecularly dissimilar agent. Attempts should be made to identify and treat potential underlying diseases. In life-threatening cases, whole blood or platelet rich plasma transfusion is indicated. Dexamethasone (0.05-0.1 mg/kg IV q24h) is generally indicated to decrease Fc binding, phagocytic removal, and antibody production. When the platelet count is greater than 100,000/ $\mu$ l, the dose of steroid should be reduced 0.01 mg/kg/day with close monitoring for disease recurrence. Prednisolone (1 mg/kg IM q12h) may be attempted, but not all horses respond favorably to this protocol. Steroids should not be discontinued until the platelet count has been within normal limits for at least 5 days. If steroid therapy has been implemented for greater than 2 weeks, every-other-day administration should be implemented in the tapering dose protocol. Splenectomy has been reported in humans and dogs, but long-term outcome has not been reported in the horse. The vinca alkaloid, vincristine at a dose of 0.01 to 0.025 mg/kg IV weekly, has been used with steroid therapy to increase the peripheral platelet count with some success. Because vin-

cristine has immunosuppressive activities, neutropenia may develop; this is an indication for drug discontinuation. Although anecdotal evidence suggests some improvement of thrombocytopenia with the use of azathioprine (3-5 mg/kg PO q24h) and cyclophosphamide (300 mg/m<sup>2</sup> body surface area), no data are currently available to support their routine use. Complications associated with immunosuppressive therapies may include laminitis and profound immunosuppression that lead to secondary sepsis. Concentrated immunoglobulin therapy has been used for human patients with profound IMTP. The mechanism is multifaceted; however, blocked Fc receptor binding, steric hindrance of immune complex adherence, enhanced T lymphocyte suppressor activity, and reduced B lymphocyte function are proposed actions of excessive Ig administration. The recommended dose is 200 to 1000 mg IgG/kg per day for 2 to 5 days or approximately 6 L plasma per dose for a 450-kg horse. Although equine plasma transfusion carries a reduced risk of adverse effects when compared with glucocorticoids, the cost associated with treatment may be prohibitive. A less expensive alternative to equine plasma is lyophilized equine IgG (Lyphomune, Diagon Corporation; Rockville, Md.); however, its use in IMTP has been limited in horses.

Whole blood transfusion or platelet-rich plasma can be used to treat thrombocytopenic patients that have persistent hemorrhage. Platelet-rich plasma is harvested by centrifuging fresh blood for a short time at a slow speed (3 to 5 minutes at 250 g). Blood or plasma should be collected into plastic bags because glass activates platelets, and either product should be used immediately. Platelet transfusion is a transient life-saving procedure, and the ultimate outcome depends on the individual case.

Cases of secondary IMTP that result from drug administration often resolve rapidly after drug withdrawal, except in cases associated with chrysotherapy (gold salts), which may require months to years to resolve. Many cases of equine IMTP recover in approximately 3 to 4 weeks. Cases that are secondary to EIA or neoplasia carry a poor to grave prognosis. Reports exist in which chronic recurrent thrombocytopenia has continued for an extended period of time and required intermittent steroid administration.

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## CHAPTER 6.6

# Hemostatic Disorders

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Coagulation and the formation of platelet-mediated hemostasis are important defense mechanisms against hemorrhage. Disruption between the balance of fibrinolysis and coagulation results in hemorrhagic and/or thrombotic disease. Hemostatic disorders can be inherited or acquired in origin. Inherited coagulation disorders are rare and primarily affect the intrinsic coagulation pathway. Acquired hemostatic disorders involve blood vessels, platelets, or clotting factors. The most common acquired coagulation dysfunctions in the horse are immune-mediated vasculitis and disseminated intravascular coagulation (DIC).

### CLINICAL SIGNS

Clinical signs related to platelet dysfunction or coagulation factor abnormalities consist of unexpected bleeding after minor trauma or surgery, petechiae, ecchymoses, hyphema, epistaxis, melena, hematoma, and hemorrhage. Hemarthrosis, hemoabdomen, and hemothorax can occur in either acquired or inherited hemostatic dysfunction. Clinical signs associated with hypercoagulation include jugular vein thrombosis or thromboembolic disease that affects the gastrointestinal tract, pulmonary, renal, cerebral, or the digital vasculature. In general, horses with vascular or platelet defects will develop petechiae of the mucous membranes and/or superficial bruising of the skin. Bleeding tends to occur immediately after minor trauma or surgery; once it stops, however, it tends not to recur unless trauma occurs at the same site. In contrast, horses that have a clotting factor defect tend to develop hematomas, hemarthrosis, hemoperitoneum, or hematuria. Posttraumatic bleeding tends to be delayed but can recur in horses with coagulation abnormalities.

### DIAGNOSTIC APPROACH

Recognition of clinical signs and basic laboratory tests can narrow the list of differential diagnoses (Figures 6.6-1 and 6.6-2). Bleeding times are difficult to measure accurately but would be normal with clotting factor deficiency and abnormally prolonged with platelet function defects, thrombocytopenia, von Willebrand's disease, or vascular disease. Initial characterization of coagulopathy can be achieved by performing a platelet count (see Figures 6.6-1 and 6.6-2). Blood collected in EDTA is usually adequate; however, falsely low platelet counts can occur from *in vitro* clumping. Pseudothrombocytopenia should be suspected when platelet clumping is reported on the morphologic assessment and/or if the mean platelet volume (MPV) is

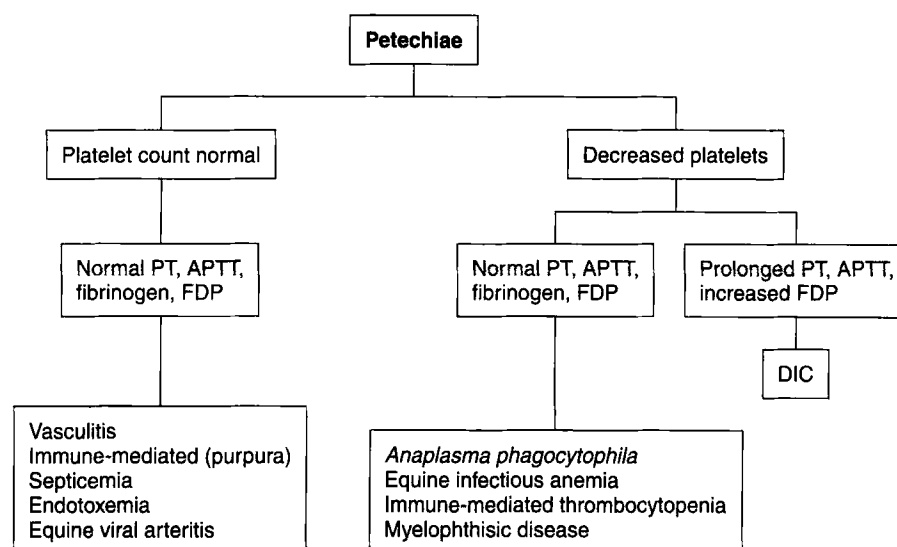
increased. In this scenario, the blood should be collected into 3.8% sodium citrate (9 parts blood to 1 part citrate) to obtain a more accurate measurement.

Further characterization of coagulopathy involves measurement of activated partial thromboplastin time (APTT; intrinsic and common pathways), prothrombin time (PT; extrinsic and common pathways), fibrin degradation products concentration (FDP) and fibrinogen (see Figures 6.6-1 and 6.6-2). Sample collection for these tests must be very accurate to acquire valid results. The blood sample must be obtained by a direct venipuncture. Precisely 9 parts of blood is mixed with 1 part 3.8% trisodium citrate anticoagulant. The blood must be mixed thoroughly in the tube. Ideally the tests should be performed within 30 minutes of sample collection. If immediate analysis is not available, the plasma should be separated from the cells by centrifugation and is stable at 4° C (39° F) for 48 hours or is frozen. Special tubes containing thrombin and aminocaproic acid are required for quantitative analysis of FDP and are commercially available (Wellcome Diagnostics; Greenville, N.C.). Age, assay type, and time-matched controls are extremely important to accurately interpret the results. For example, healthy neonatal foals have several unique differences in comparison to adults, such as significantly greater FDPs and longer PT and APTT. Thus if a coagulation profile from a foal was compared to an adult as the control, the values may be erroneously interpreted as abnormal. In general, when using a healthy cohort as a reference, patient values greater than 30% of the healthy control are significant.

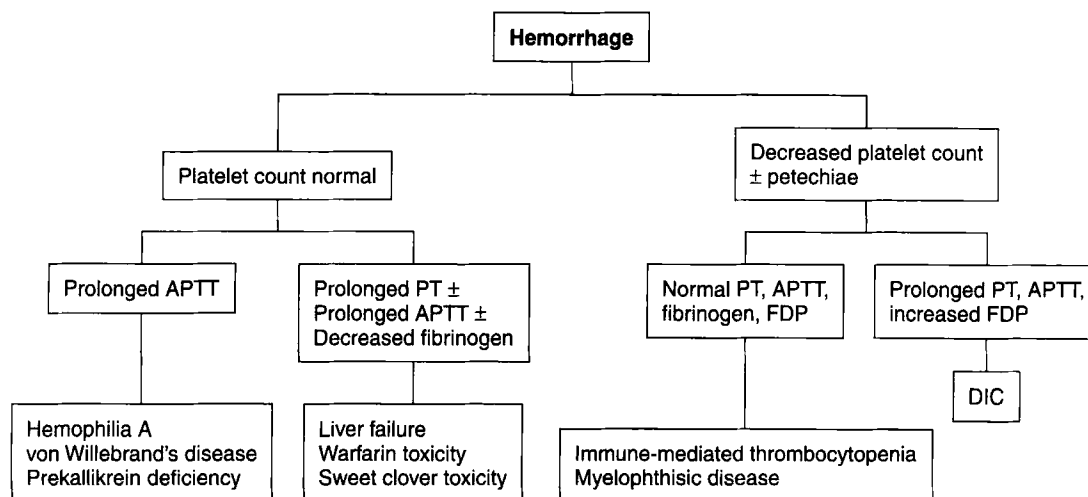
### INHERITED COAGULATION DISORDERS

#### Hemophilia A (Factor VIII Deficiency)

Hemophilia A is caused by deficiency of factor VIII and is the most common inherited coagulation disorder of horses. It has been reported in the Thoroughbred, Standardbred, Quarter Horse, and Arabian. Only males are affected, and their life expectancy is short (6 months to 3 years). Because the disease is X-linked-recessive, half of the male offspring of carrier mares will inherit the deficiency, and half of the female offspring will be carriers. The diagnosis is determined by the presence of unexpected, recurrent hemorrhage in a young male with an abnormally prolonged APTT and reduced factor VIII:C activity. Administration of fresh plasma can temporarily replace the clotting factor deficiency, but the effect only lasts for hours to days. Most horses die or are euthanized because of the lack of long term treatment and curative options.



**Figure 6.6-1** Diagnostic approach to petechiae. *PT*, Prothrombin time; *APTT*, activated partial thromboplastin time; *FDP*, fibrin degradation products concentration; *DIC*, disseminated intravascular coagulation.



**Figure 6.6-2** Diagnostic approach to hemorrhage. *PT*, Prothrombin time; *APTT*, activated partial thromboplastin time; *FDP*, fibrin degradation products concentration; *DIC*, disseminated intravascular coagulation.

### von Willebrand's Disease

von Willebrand's disease (vWD) is a rare disorder that has been reported in the Quarter Horse and Thoroughbred. The disease is caused by quantitative or qualitative defects in von Willebrand factor (vWF). This results in a defect in primary hemostasis that affects the formation of the platelet plug. Clinical signs include epistaxis and bleeding from the skin or mucous membranes after mild trauma or surgery. vWD should be suspected in young horses that exhibit clinical signs with normal to abnormally prolonged APTT and bleeding times but normal PT and platelet counts. Diagnosis is confirmed by specific assays for vWF—including vWF:Ag concentration (enzyme-linked immunosorbent assay [ELISA]), ristocetin cofactor

activity, and Factor VIII:C. Episodes of bleeding in a broodmare and her colt with vWD were successfully managed with administration of plasma. This treatment is only palliative. In humans and dogs, vWD has been treated with desmopressin (deamino-8-D-arginine vasopressin [DDAVP]), a synthetic vasopressin analogue that increases the release of vWF from the endothelial cells. This therapy is currently cost-prohibitive in horses.

### Prekallikrein Deficiency

Prekallikrein is a contact factor that becomes activated when plasma interacts with a negatively charged surface that initiates the intrinsic coagulation cascade. Prekallikrein



deficiency has been documented in families of Belgian and Miniature Horses affecting both males and females. The defect is an autosomal recessive trait in humans. It is thought that horses with more severe signs are homozygous and those not affected are heterozygous for the genetic defect. The clinical signs range from minimal, to excessive hemorrhage after castration in one Belgian horse. Diagnosis is determined by an abnormally prolonged APTT and specific measurement of prekallikrein activity.

### Protein C Deficiency

Protein C is a vitamin K-dependent protein with both anticoagulant and profibrinolytic activities. Protein C deficiency results in a hypercoagulable state that has been reported in a 2-year-old Thoroughbred colt. This colt developed recurrent venous thrombosis, nephrolithiasis, and severe renal disease and had a normal platelet count, PT, APTT, and increased FDPs. In humans, hereditary defects of protein C have been determined by using antigenic and functional assays of protein C. In the reported equine case, protein C activity was reduced, but protein C antigen concentration was normal, thus suggesting that the protein C defect in this colt was functional.

## ACQUIRED COAGULATION DISORDERS

### Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is the most common hemostatic dysfunction in the horse. DIC is an acquired process in which activation of coagulation causes widespread fibrin deposition in the microcirculation resulting in ischemic damage to tissues. Hemorrhagic diathesis occurs as a result of consumption of procoagulants or hyperactivity of fibrinolysis. In normal coagulation, thrombin activates the conversion of plasma soluble fibrinogen to the insoluble fibrin, which forms a clot. Simultaneously, the fibrinolytic system is activated to prevent tissue ischemia that would occur from persistent fibrin clots. The fibrinolytic protein that is primarily responsible for limiting fibrin clot formation and providing a mechanism for clot removal is plasmin. Antithrombin III and protein C also minimize clot formation by inhibiting the actions of thrombin and as well as some of the other clotting factors. In DIC, antithrombin III and protein C become depleted as a result of overzealous activation of coagulation. This results in excessive, unchecked thrombin and clot formation, which in turn activates plasmin. FDPs are formed when plasmin degrades fibrin. As the FDPs begin to accumulate in the circulation, they contribute to the coagulopathy by inhibiting thrombin activity and by causing platelet dysfunction. The end result is the dynamic combination of disseminated thrombosis at the same time that clotting factor consumption and fibrinolysis potentiate bleeding.

DIC is not a primary disease; it occurs in conjunction with diseases that generate excessive procoagulant activity in the blood. Diseases related to the gastrointestinal system (e.g., strangulating obstruction, colitis, enteritis), sepsis, renal disease, hemolytic anemia, and neoplasia are the most common primary diseases associated with DIC. In

one study, 96% of the horses that developed DIC over a 5-year period were diagnosed with colic that required surgical intervention. Horses with devitalized intestine that required resection and anastomosis were more likely to develop DIC than those horses in which resection and anastomosis was not required. Because endotoxin is a prominent feature of ischemic or inflammatory disease of the equine gastrointestinal tract, it is a logical conclusion that endotoxemia is the underlying pathophysiologic event that most commonly triggers DIC. Endotoxin can initiate DIC by several mechanisms: (1) direct damage to the endothelium, thereby releasing tissue factor; (2) induction of tissue factor expression and cytokine synthesis by mononuclear phagocytes; (3) direct activation of factor XII; (4) stimulation of thromboxane A<sub>2</sub> synthesis by platelets which promotes irreversible platelet aggregation; and (5) inhibition of fibrinolysis by increasing production of plasminogen activator inhibitor.

### Clinical Signs

Clinical signs of DIC range from mild thrombosis and ischemic organ failure to petechiae and hemorrhage. In contrast to humans, frank hemorrhage associated with DIC is rare. Petechial or ecchymotic hemorrhages of the mucous membranes or sclerae, epistaxis, hyphema, and melena can occur. Hypoperfusion and microvascular thrombosis lead to focal or widespread tissue damage and culminates in colic; laminitis; and signs of renal, pulmonary, and cerebral disease. Peripheral veins are susceptible to spontaneous thrombosis as well as increased thrombus formation after catheterization or simple venipuncture. Clinical signs of the primary underlying disease may overshadow the initial signs of DIC.

### Diagnosis

A single test cannot confirm DIC. The presence of clinical signs—thrombocytopenia, prolonged APTT and PT, and an increase in FDP concentration ( $>40 \mu\text{g/ml}$ )—is consistent with DIC. In the early stages of DIC, FDPs may not be increased. Monitoring changes over time can help decipher difficult cases, as thrombocytopenia and prolongation of the PT are frequently the only abnormalities initially detected. Hypofibrinogenemia is an uncommon finding in the horse; in fact, fibrinogen concentration may be increased, depending on the duration of the underlying primary disease. Reduced antithrombin III activity ( $<80\%$  normal) also supports a diagnosis of DIC.

### Treatment and Prognosis

Determining the correct therapy for DIC is difficult and controversial. Identification and treatment of the underlying disease process is paramount. Intravenous fluid therapy is necessary to maintain tissue perfusion and combat shock. If a septic process is present, antimicrobials are indicated. If a strangulating intestinal obstruction is present, immediate surgical correction is warranted. Minimizing the effects of endotoxemia may attenuate the disease process (see Chapter 3.7: "Endotoxemia"). Flunixin meglumine ( $0.25 \text{ mg/kg IV q8h}$ ) will mitigate the detrimental effects of eicosanoids. Corticosteroids are contraindicated because they potentiate the vasoconstrictive effect of catecholamines and reduce the activity of the mononuclear

phagocyte system, which exacerbates coagulopathy by enabling FDPs to accumulate.

Fresh plasma therapy (15-30 ml/kg of body weight) is indicated with severe hemorrhage. It should be noted that administration of plasma could exacerbate thrombosis by supplying more clotting factors to "fuel the fire." Fresh whole blood can be given if anemia is present from blood loss. Although its use remains controversial, administration of heparin (20 to 100 U/kg SQ q8-12h) in conjunction with fresh plasma may minimize clot formation by potentiating the anticoagulative effects of antithrombin III. Thus if heparin therapy is to be used, adequate antithrombin III must be present. Heparin can cause thrombocytopenia, hemorrhage, and reversible erythrocyte agglutination. If heparin is used, the packed cell volume should be closely monitored for a sudden decline. Low-molecular-weight heparin (Fragmin, Kabi Pharmacia AB; Stockholm, Sweden; 50 U/kg SQ q12h) does not cause agglutination of equine erythrocytes, but its use may be cost-prohibitive. The prognosis for DIC depends on the severity of the underlying disease and the response to therapy. In general, the prognosis is guarded to poor. In humans, the mortality rate is 96% when the antithrombin III activity falls below 60%.

### Warfarin and Sweet Clover Toxicosis

Horses may develop hemorrhagic diathesis after consuming warfarin for therapeutic reasons, rodenticides, or moldy sweet clover (*Melilotus* spp.). Warfarin has been used for treatment of thrombophlebitis and navicular disease. Combination of warfarin with other protein-bound drugs, such as phenylbutazone, results in toxic accumulation in the plasma. Sweet clover hay or silage that is improperly cured can contain dicumarol. The toxin is not present in the living plant. The pathogenesis of warfarin and sweet clover toxicosis are identical. Dicumarol and warfarin competitively inhibit vitamin K, which is necessary for the production of clotting factors II, VII, IX, X.

The clinical signs of warfarin or dicumarol toxicosis include hematomas, hematuria, epistaxis, and ecchymoses of the mucous membranes. Absence of petechial hemorrhages can distinguish warfarin and dicumarol toxicity from DIC. The diagnosis is made based on history of exposure and laboratory data. Clinical pathology reflects prolonged PT first because the plasma half-life of factor VII is shorter than the other clotting factors. The APTT becomes prolonged, but the platelet count remains normal.

Treatment for warfarin toxicity may only require discontinuation of the drug. If accidental exposure to rodenticides or dicumarol occurs, treatment with vitamin K<sub>1</sub> (0.5 to 1 mg/kg of body weight SQ q6h) 3 to 5 days is recommended. Therapy should be guided by measuring PT. Vitamin K<sub>3</sub> causes acute renal failure and should not be given to horses. In an acute crisis, plasma or a whole blood transfusion may be indicated.

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## CHAPTER 6.7

# Blood and Blood Component Therapy

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Equine patients suffer circulatory collapse secondary to acute or chronic blood loss, significant hypoalbuminemia, and septic shock. Management of these critical patients is centered on reestablishing blood pressure and oxygen supply to vital organs such as the brain, kidneys, and liver. Commonly used therapies include crystalloid and colloid administration. Infusion of crystalloids in large volumes tends to lower oncotic pressure because of its dilutional effect yet transiently increases intravascular hydrostatic pressure. In contrast, colloid infusion results in increased plasma oncotic pressure because of its supply of large osmotically active molecules that are retained within the vasculature. Hence fluid resuscitation with colloids may result in greater improvements in cardiovascular status than with crystalloids. Natural colloids include whole blood, blood components, and plasma. Synthetic colloids are hetastarch, dextran, gelatin, and polymerized hemoglobin.

### NATURAL COLLOID THERAPY

#### Whole Blood Transfusion

When deciding if a whole blood transfusion is warranted, several factors should be considered—including the severity and cause of anemia, the short life-span of transfused red blood cells (RBC), and compatibility testing (cross-matching). A whole blood transfusion is indicated in horses with a packed cell volume (PCV) at or below 12% secondary to acute blood loss or hemolysis. Similarly, whole blood transfusion is indicated in a patient with a PCV less than or equal to 8% that results from chronic blood loss or hemolysis. Admittedly, these values are not absolute, and the patient's overall clinical condition should be considered along with determination of whether blood loss or hemolysis is ongoing.

In addition to evaluating the severity and cause of the anemia, the short lifespan of transfused RBCs should be considered. Allogenic equine erythrocytes are removed from the circulation by the mononuclear phagocyte system within 4 days of transfusion as the result of the development of serum antibodies against nonhost erythrocyte antigens within 3 to 10 days in nearly half of horses after a single transfusion. Thus any necessary subsequent transfusions should be performed with caution if given more than 3 days after the initial transfusion.

Horses display a high degree of blood group polymorphism. At least 30 different erythrocyte antigens (alloantigens) that make up multiple blood types (A, C, D, K, P, Q, and U) account for the 400,000 or so blood phenotypes in horses. Hence identification of a perfect match between a donor and recipient is nearly impossible. However, suitable compatibility may be determined by prior blood-typing of the donor and agglutination cross-match testing. Prior knowledge of the donor's blood type is helpful to avoid donors that are carrying the alloantigens Aa and Qa. These alloantigens are considered the most immunogenic, and transfusion of blood that contains these antigens may result in severe hemolysis. The Quarter Horse and Belgian breeds carry a low frequency of Aa and Qa alloantigens. The saline agglutination test can be divided into major and minor cross-matching. The major cross-match combines washed erythrocytes from the donor and serum from the recipient and is followed by agglutination testing. In contrast, the minor cross-match combines donor serum with erythrocytes from the recipient and is followed by testing for agglutination. Unfortunately, such testing does not provide information regarding hemolyzing antibodies (hemolysin), which, if present, will cause severe hemolysis of transfused RBCs. Testing for hemolysins requires adding exogenous complement from rabbit serum to the reaction mixture, and such testing is limited to few laboratories because of the special handling and storage required of rabbit serum. Compatibility testing should precede transfusion; however, that is not always possible. In the absence of donor blood-typing, cross-matching, or testing for hemolysins, the ideal equine blood donor is an adult gelding that is negative for equine infectious anemia virus and has never received a blood or plasma transfusion. In addition, first-time transfusion of whole blood to a patient that has not received previous blood products or cross-matched is usually well-tolerated. In cases of blood loss into a body cavity, autotransfusion of blood may be considered if the blood can be collected aseptically.

Although whole blood transfusions may significantly improve the patient's immediate condition, they are not without complications. As previously mentioned, the short half-life of transfused RBCs and the development of alloantibodies limit the extent of long-term benefits from whole blood transfusions. In addition, blood transfusions

suppress bone marrow response to anemia by reducing the production of erythropoietin by the kidneys. The normal bone marrow begins to replace lost cells within 5 days. Hence whole blood transfusions provide only temporary improvements of oxygen supply to vital tissues. Thus even after a whole blood transfusion, determination and correction of the cause of the anemia remains critical.

### Whole Blood Collection

Whole blood is collected from the donor into sterile, plastic collection bags or sterile glass containers that contain acid-citrate-dextrose (ACD) or citrate-phosphate-dextrose (Baxter; Deerfield, Ill.). The desired ACD-to-whole blood ratio is approximately 1:10. Depending on individual preferences, sterile glass containers may be better suited for more efficient collection of whole blood because of the negative pressure while under vacuum. However, once they are filled, they are heavy; if they are dropped, all of the contents may be lost. Regardless of the collection container, the collection procedure is aseptically performed through an intravenous catheter or a large bore needle connected to an extension set. Determination of the total blood volume to collect and transfuse depends on the size of the donor and the estimated blood loss of the recipient. An average size horse (450 kg) with a PCV of 35% to 40% can provide approximately 20% (8-10 L in an adult horse) of its blood volume every 30 days. Generally, 20% to 30% of the recipient's total blood volume (7-11 L in a 450-kg horse) is adequate to recover oxygen supply to vital tissues until bone marrow has an opportunity to respond. Alternatively, if whole blood transfusion is warranted and an estimate of blood loss is not accurate, 15 ml/kg (6-8 L in a 450-kg horse) of whole blood may be administered. Once it is collected, using whole blood immediately is best, yet it can remain stable at 4° C for 2 to 3 weeks once the ACD is added.

### Blood Administration

Whole blood is filtered before administration and is transfused into the recipient through an aseptically placed jugular catheter. Initially (5-10 min), the administration rate should be slow (0.1 ml/kg) to observe for any signs of adverse reactions. These include tachypnea, dyspnea, restlessness, tachycardia, piloerection, muscle fasciculations, or sudden collapse. Subsequently, the transfusion rate may be increased to but not exceed 20 ml/kg/hour. If severe adverse reactions occur, the transfusion should be terminated, and epinephrine (0.01 to 0.02 ml/kg, 1:1000) along with isotonic fluids should be administered. Alternatively, if only mild reactions occur, the transfusion rate may be slowed and corticosteroids or nonsteroidal antiinflammatories administered.

### Blood Component Therapy

Administering concentrates of specific equine plasma components rather than whole blood may be more appropriate for treating deficiencies of granulocytes, platelets, or erythrocytes. This is especially true for patients with a deficiency in a cell type due to destruction rather than blood loss.

These horses do not have a deficiency in blood volume but rather a deficiency in the specific constituents. Hence a whole blood transfusion may predispose them to fluid overload, whereas administration of the specific components that are deficient may be more appropriate. Centrifugation apheresis provides a method for concentrating granulocytes, platelets, and erythrocytes from whole blood. In addition to these cell types, other blood components such as immunoglobins and clotting factors may be concentrated and administered. Concentrated, lyophilized immunoglobulin (Lyphomune, Diagon Corporation, Rockville, Md.) is commercially available for treatment of failure of passive transfer in foals, selective deficiencies of immunoglobulin, and treatment of immune-mediated disorders. Cryoprecipitate—a mixture of factor VIII:C, fibrinogen, and fibronectin—is used for treatment of hemophilia in dogs and people but is not readily available or affordable for use in horses. The collection of whole blood and administration of the blood components should follow the same guidelines as discussed previously. Furthermore, aseptic handling of the blood components during the centrifugation apheresis is critical to prevent bacterial contamination before administration.

### Alternatives to Blood Component Therapy

In addition to transfusion, several alternative products have been used to treat granulocyte deficiencies such as neutropenia. These products include hemopoietic growth factors such as recombinant canine and bovine granulocyte-colony stimulating factor. In one study, normal foals that were given bovine granulocyte-colony stimulating factor experienced an increase in neutrophil count without apparent adverse effects. A second study in foals found an increase in bone marrow cellularity and increased myeloid activity after treatment with canine recombinant granulocyte-colony stimulating factor. The efficacy of these products is suggested by these studies; however, more work is needed to develop a therapeutic plan for horses of all ages. Administration of human recombinant erythropoietin to horses can result in severe, sometimes fatal, anemia.

### Plasma Transfusion

Horses that are suffering from declining intravascular oncotic pressure due to protein deficiency and neonatal foals that are suffering from failure of passive transfer are candidates for plasma administration. Foals require 1 to 2 L (20-40 ml/kg) of plasma to adequately increase IgG levels, and hypoproteinemic adult horses (450 kg) require 6 to 8 L of plasma to improve oncotic pressure. In general, administration of 7 L of equine plasma that contains 7 g/dl of protein will result in a 1 g/dl increase in total protein.

Plasma retains several advantages over synthetic colloids as a source of functional proteins (clotting factors), immunoglobins, and complement. However, disadvantages to plasma include its poor ability to increase oncotic pressure and the expense of product. Plasma can be purchased from commercial supplier (Lake Immunogenics, Ontario, N.Y.; Veterinary Dynamics, Inc., Chino, Calif.; Immvac, Inc., Columbia, Mo.; Veterinary Immunogenics,

LTD, Cumbria, England) or can be collected from whole blood that has been centrifuged or allowed to settle at room temperature for 1 to 2 hours, followed by removal of the settled RBCs by gravity flow. The collection of whole blood and administration of the plasma should follow the same guidelines discussed previously. Furthermore, aseptic handling of the blood components during plasma separation is critical to prevent bacterial contamination before administration. Because of the high risk of contaminating the plasma with large volumes of whole blood, storage of liter bags of commercially available equine plasma for future use at 0° C for up to 1 year might be ideal. In addition to normal plasma, hyperimmune plasma from horses that have been immunized against the etiologic agents responsible for diseases such as *Rhodococcus pneumoniae*, salmonellosis, and botulism are commercially available. (Lake Immunogenics, Veterinary Dynamics, Inc., Immvac, Inc., Veterinary Immunogenics, LTD). The efficacy of these products remains unknown; however, some evidence suggests that the incidence or severity of *Rhodococcus pneumoniae* may be lessened in foals that receive hyperimmune plasma.

## SYNTHETIC COLLOID ADMINISTRATION

As an alternative to natural colloid infusion, synthetic colloids (hetastarch, dextran, gelatin, and polymerized hemoglobin) can be used to treat hypovolemic and hypooncotic conditions in horses. Hetastarch is a synthetic colloid composed predominately of amylopectin. It is available as a 6% hetastarch solution in physiologic saline and is commonly used in horses in circulatory shock and to treat low oncotic pressure secondary to hypoalbuminemia. The recommended dose of hetastarch is 5 to 15 ml/kg IV for 2 to 3 days. Interestingly, infusion of hetastarch does not result in an increase in refractive total serum solids but rather in a decline caused by the dilution of intravascular proteins. Hetastarch treatment has several advantages over other colloid infusion. The large molecules in hetastarch are less likely to extravasate through the intercellular junctions, thus providing a positive colloidal

effect for a prolonged period of time. Furthermore, the large molecules may act as a plug to prevent further leakage of albumin into the interstitial space. Hetastarch has been associated with the development of coagulopathy in some species, but this appears to be a rare complication.

Additional synthetic products that are just beginning to find their place in veterinary medicine are hemoglobin-based oxygen carriers such as Oxyglobin (30 ml/kg body weight, IV; Biopure, Cambridge, Mass.). Oxyglobin contains cross-linked hemoglobin molecules that circulate in plasma and transport oxygen to tissues upon infusion. These products have been developed to overcome problems associated with transfusion of allogeneic blood and to treat severe anemia. Preliminary studies in dog and rat models of acute hemorrhage indicate cardiovascular benefit. In addition, preliminary data in foals found Oxyglobin advantageous because of its immediate effect on oxygen tension. Unfortunately, the lifespan is approximately 24 hours, and whole blood transfusion would likely be necessary the following day. These products may be of limited use in horses because of the high cost.

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## CHAPTER 6.8

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# Polycythemia

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**P**olycythemia, or erythrocytosis, is an increase in red blood cell mass. Relative polycythemia, or hemoconcentration, is common in horses and occurs when plasma volume is decreased because of conditions such as dehydration or endotoxemia. Splenic contraction may cause transient polycythemia. Absolute polycythemia indicates an increased red cell mass in the absence of plasma volume change. Primary absolute polycythemia occurs when red cell mass increases without concurrent increase in erythropoietin concentrations. This condition is exceptionally rare but has been reported in the horse.

Secondary absolute polycythemia reflects a bone marrow response to increased erythropoietin production that results in polycythemia. Examples include congenital cardiac anomalies such as tetralogy of Fallot or certain ventricular septal defects in which hypoxia is induced by right-to-left shunting. Several case reports document polycythemia secondary to hepatic disease, including neoplasia—specifically, chronic active hepatitis, obstructive cholelithiasis, hepatoblastoma in a two-year-old Thoroughbred filly, and hepatocellular carcinoma in a yearling crossbred Arabian filly.

### CLINICAL SIGNS AND DIAGNOSIS

Nonspecific clinical signs associated with polycythemia in horses include lethargy, weight loss, and mucosal hyperemia. Increased blood viscosity impairs oxygen delivery to tissues when the packed cell volume exceeds 60%. At this point, additional clinical signs—such as abnormal mentation, epistaxis, tachycardia, and tachypnea—may become apparent. Because polycythemia typically occurs secondarily to an underlying disease, clinical signs related to the primary disease process often overshadow signs of polycythemia.

Diagnosis is based on measurement of persistently increased PCV, hemoglobin concentration, and red blood cell count in the face of normal plasma volume. The di-

agnostic plan should include arterial blood gas determination, cardiopulmonary examination, complete blood chemistry evaluation, and bone marrow assessment. Biopsy is required to measure equine erythropoietin and is not routinely available.

### TREATMENT

Phlebotomy is indicated when the PCV remains persistently above 50%. Ten to 20 ml of blood/kg are removed and replaced by an equal volume of balanced polyionic fluid. This procedure is repeated as needed, based on serial measurement of PCV. Hydroxyurea has been used in dogs and humans with polycythemia, but its utility in the horse is unknown. (A proposed protocol is provided in the third edition of this text, p. 516.) If an underlying disease is identified, appropriate treatment measures should be instituted immediately. Unfortunately, most diseases associated with secondary absolute polycythemia carry a grave prognosis.

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CHAPTER 6.9

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# Lymphoproliferative and Myeloproliferative Disorders

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**L**eukemia is the abnormal proliferation of hematopoietic cells that encompasses both lymphoproliferative and myeloproliferative disorders and is considered rarer in the horse than in other species. Leukemia can be classified based on the (1) type of abnormal cell: lymphoid or myeloid; (2) degree of tumor differentiation: acute or chronic; and (3) number of specific types of abnormal cells that are circulating in the peripheral blood: aleukemic, subleukemic, or leukemic. In addition, tumor cells can be further characterized by histochemical and immunohistologic methods. The lymphoproliferative (lymphoma, lymphoid leukemia, and plasma cell myeloma) and myeloproliferative (the myeloid leukemias and erythrocytosis) disorders of the horse are reviewed in this chapter.

## LYMPHOMA

*Lymphoma* is the general term denoting malignant transformation of lymphoid cells, but it is often used in equine medicine in place of the term lymphosarcoma, which is specifically the malignant transformation of lymphoid cells into solid (or sarcomatous) tumors. Lymphoid leukemia (or “true” leukemia) denotes the malignant transformation of lymphoid cells within the bone marrow. Both forms of lymphoid neoplasia may be accompanied by circulating neoplastic cells.

Lymphoma is one of the most common internal neoplasms of the horse, but the prevalence of lymphoma in horse populations is relatively low—ranging from 0.002% to 0.05%, based on United States abattoir surveys and from 0.2% to 3.0%, based on necropsy surveys. No established risk factors for equine lymphoma exist, and the etiology is unknown. A breed or sex predilection does not appear to be a factor, and the majority of patients are between 4 and 10 years of age. However, individual cases of lymphoma in a fetus and in horses younger than 1 year or older than 20 years of age have been reported.

## Clinical Signs

A diverse spectrum of clinical signs has been associated with lymphoma. The signs and progression of disease relate to the sites of tumor involvement and are not specific to lymphoma. The most common clinical signs are decreased appetite, depression, weight loss, fever, lymphadenopathy, and dependent edema. In a study of 20 cases of lymphoma confirmed by histology, the clinical findings included—in de-

scending order of frequency—weight loss, fever, peripheral lymphadenopathy, abdominal mass, upper or lower respiratory signs, ocular signs, colic, and diarrhea.

Numerous lymphoma tumor locations have been reported and include peripheral and internal lymph nodes, spleen, liver, kidney, intestine, heart, lung, nasopharynx, eye and adnexa, skeletal muscle, skin, reproductive organs, and central and peripheral nervous system. Four anatomic forms of lymphoma are well described: multicentric—50%; alimentary—19%; mediastinal—6%; and extranodal—25%. Combinations of these four classic forms of lymphoma occur in approximately 50% of cases.

Multicentric, or generalized, lymphoma is the most commonly reported form and involves multiple peripheral and internal lymph nodes and other organs. The most commonly involved peripheral lymph nodes are the mandibular, caudal cervical, retropharyngeal, and superficial inguinal. The most commonly involved abdominal lymph nodes are the mesenteric, colonic, and deep iliac. Splenomegaly occurs in 25% of the cases, and hepatomegaly or perirenal masses are found infrequently. The multiple sites of involvement probably represent metastasis via the blood and lymphatic circulatory systems. Notably, this is the most common form to be associated with circulating neoplastic lymphocytes, referred to as the “leukemic phase” of lymphoma. Clinical signs reflect dysfunction of affected organs, and the course of the disease is typically rapid once signs become evident.

The alimentary type is the most acute form of lymphoma. It causes rapid deterioration and involves the small intestine and associated mesenteric lymph nodes. Distant metastasis appears slow to develop. Alimentary lymphoma is commonly detected in horses from 2 to 5 years of age. Signs are considered nonspecific and include weight loss, decreased appetite, fever, dependent edema, and diarrhea or abdominal pain of varying severity and duration. Affected horses may have a blunted oral glucose tolerance response and reduced serum albumin concentration, which suggests intestinal malabsorption. Immune-mediated hemolytic anemia and hyperglobulinemia have also been reported to accompany this condition.

Lymphoma of the mediastinal lymph nodes typically occurs in adult horses. The most common clinical signs are referable to compression of intrathoracic structures and include pleural effusion, tachypnea, dyspnea, and dependent edema. Less common findings include a persistent cough, tachycardia, jugular vein distention, and fore-

limb lameness. Neoplastic cells may be observed in the pleural fluid and the paraneoplastic syndrome of hypercalcemia has been associated with this form of lymphoma.

The most common extranodal sites of tumor development are—in descending order—the skin, upper respiratory tract, eyes or adnexa, and central nervous system. Lymphoma of the skin—the cutaneous form—is the least common form of lymphoma in horses, although it represented the most common form in one report. Tumors are readily identified as nonpainful, dermal, or subdermal masses that are firm and well circumscribed and may be haired, nonhaired, or ulcerated. Horses may have a solitary mass or multiple masses that range in size from a few millimeters up to several centimeters in diameter. The most commonly affected regions include the shoulder, perineum, axilla, and trunk. Clinical signs are referable to internal metastasis and may not be present during the initial examination. Tumors may develop rapidly or slowly and may spontaneously regress and reappear. However, cutaneous lymphoma generally manifests as a slowly progressive extension of an internal malignancy and involves multiple or single, nonulcerated dermal or subdermal masses of neoplastic lymphocytes (i.e., a sarcomatous form). The most rare form of cutaneous lymphoma is termed mycosis fungoides, which differs from the sarcomatous form in that it represents a diffuse infiltration with neoplastic lymphocytes of the dermis or subdermis. This rare form of cutaneous lymphoma is also chronic and progressive and, without appropriate histologic examination of the skin, may be easily mistaken for other diffuse non-neoplastic dermatoses.

Extranodal lymphoma of the eye or adnexa most commonly involves the palpebral conjunctiva and eyelids and may be associated with exophthalmus, exposure keratitis, uveitis, chemosis, and conjunctivitis. Lymphoma has been occasionally reported to involve the upper respiratory tract, thus causing signs of upper airway obstruction with and without nasal discharge. A single recent report involved tumor infiltration of the tongue. Reports of peripheral nerve sheath and epidural infiltration also exist and may be considered rare differentials for lameness and ataxia, respectively. Metastatic periarticular involvement that causes lameness has also recently been reported.

## Diagnosis

Diagnosis of lymphoma can be difficult, and *ante mortem* confirmation occurs in less than 60% of cases. The key to *ante mortem* diagnosis is a persistent diagnostician. Neoplasia must always be considered in an adult horse with recurrent inflammatory and febrile episodes that are unresponsive to antimicrobial therapy. The physical examination should include transrectal abdominal palpation and careful thoracic auscultation and percussion. However, the definitive diagnosis of lymphoma requires the observation of neoplastic cells in aspirates or biopsy specimens of lymph nodes and other masses or in centesis samples of body cavity fluids, bone marrow aspirates, or peripheral blood.

Cytologic observations consistent with neoplastic transformation of lymphoid cells include mitotic figures, prominent nucleoli, and binucleation, but evaluation of

tissue architecture is equally important in the detection of neoplastic transformation and can only be obtained with biopsy. The observation of neoplastic lymphocytes in the peripheral blood is uncommon and may be a late manifestation of lymphoma in the horse, thus indicating dissemination and bone marrow involvement. When neoplastic cells are observed in the peripheral blood, the leukemia is characterized as subleukemic or leukemic if the total white blood cell count is normal or increased, respectively. Lymphoma is aleukemic when neoplastic cells are not present in peripheral blood. Furthermore, the leukemia may be characterized by the appearance of the transformed cells: acute or lymphoblastic leukemia if immature; chronic or lymphocytic leukemia if mature.

Since publication of the last edition of this text, significant strides have been made in classifying lymphomas using antibodies to cell surface antigens (Kelley and Mahaffey, 1998; see readings list). Probably the greatest anticipated utility of immunophenotyping equine lymphomas is in the prognostication and choice of anti-neoplastic agent(s), as has been realized in human and small animal veterinary medicine. In addition, immunophenotyping should aid in determining the cell lineage of more poorly differentiated equine tumors, in the correct classification as T cell versus B cell lymphomas, in recognizing phenotypic-specific distribution patterns, and in determining the apparent proliferation rates of lymphoid tumors. For example, immunophenotyping has led to the discovery of a previously unrecognized form of equine lymphoma—the T cell-rich, B cell lymphoma, a form that appears to be prone to subcutaneous tumors. This phenotype may be a major form of lymphoma in horses and represents 11 out of 24 (or 46%) B cell lymphoma cases and about 33% of all lymphomas.

Paraneoplastic syndromes are the indirect systemic effects of cancer and may have profound consequences on disease expression. The cause of these syndromes is often unknown but generally thought to be mediated by soluble substances released from the neoplastic cells. A few of the paraneoplastic syndromes that may be relevant to horse cancer patients include cachexia, hypercalcemia, hypoglycemia, hypertrophic osteopathy, anemia, disseminated intravascular coagulation, leukocytosis, hyperproteinemia, fever, and various neurologic abnormalities. Adjunct therapy aimed at diminishing paraneoplastic syndromes may have a profound effect on patient comfort and clinical course (Ogilvie, 1998; see readings list).

Anemia is a common finding and occurs in 30% to 50% of horses with lymphoma. Typically, the anemia is mild, normochromic, and normocytic and reflects bone marrow suppression. Immune-mediated hemolytic anemia may be suspected based on a positive direct Coombs' test. Thrombocytopenia can be profound and has resulted in bleeding diathesis. The number of leukocytes and lymphocytes in the peripheral blood is often within normal limits. With leukocytosis, mature neutrophilia and increased serum fibrinogen activity are most commonly observed and indicate the presence of inflammation. Leukopenia and pancytopenia are uncommon findings.

Common alterations of plasma proteins include increased fibrinogen, total protein, and globulin concentrations. Gammopathy may reflect chronic inflammation but



may also reflect neoplastic clonal expansion of B cell lymphocytes (see later section on plasma cell myeloma). Hypoalbuminemia may occur in response to a profound gammopathy or from gastrointestinal loss and rarely from end-stage liver failure as a consequence of hepatic involvement. Both selective (immunoglobulin M [IgM]) and generalized immunoglobulin deficiencies have been occasionally associated with lymphoid neoplasia in horses. Biochemical alterations that may be seen include hypercalcemia, increased liver enzyme activity, and azotemia.

### Prognosis and Treatment

In the majority of patients, rapid deterioration follows the onset of clinical signs associated with internal disease. Horses with lymphoma limited to cutaneous involvement, however, have survived for several years with and without chemotherapeutic intervention. Immunosuppressive glucocorticoid therapy (0.02-0.2 mg/kg dexamethasone [Azium] IV, IM, or PO q24h) may be palliative for steroid-responsive malignancies and may also suppress immune-mediated sequelae, including hemolytic anemia and thrombocytopenia. Cutaneous lesions may regress in 2 to 6 weeks, at which time the dose may be gradually reduced. If glucocorticoid administration is tapered too quickly or is discontinued, more aggressive lymphoid tumors may reappear. Signs of acute laminitis have been observed during glucocorticoid therapy in equine cancer patients and were the grounds for discontinuing therapy.

Few reports discuss use of a specific antineoplastic agent in the treatment of equine lymphoma. The expense and possible toxicity of chemotherapy in the horse are the most common reasons cited for nontreatment. However, the use of a multiple-agent induction protocol in horses with lymphoma has been reported (Byrne et al, 1991 and Couto, 1994; see readings list) and is summarized here. Cytosine arabinoside (Cytosar-U; 200-300 mg/m<sup>2</sup> SQ or IM) is given once every 1 or 2 weeks. Chlorambucil (Leukeran; 20 mg/m<sup>2</sup> PO) is given once every 2 weeks. Prednisone (Deltasone; 1.1-2.2 mg/kg PO) is given every other day throughout the treatment period. Alternatively, cyclophosphamide (Cytosan; 200 mg/m<sup>2</sup> IV given once every 2-3 weeks) is substituted for chlorambucil. Antineoplastic agents are given on alternating weeks but have been given on the same day without apparent consequence. Response to induction therapy should occur within 2 to 4 weeks, but if a response is not observed, adding vincristine (Oncovin; 0.5 mg/m<sup>2</sup> IV once a week) to the induction protocol has been recommended.

With remission, the induction protocol is used for a total of 2 to 3 months and then is switched to a maintenance protocol. The first cycle of maintenance therapy increases the treatment interval for each antineoplastic agent by one week; prednisone, however, is given for the duration of therapy and is gradually reduced in dose. After 2 to 3 months on the first cycle, if the horse is still in remission, the second cycle is begun, adding one more week to the treatment intervals of each agent. Several cycles of maintenance therapy can be given; however, most horses in remission are treated for a total of 6 to 8 months.

Other reported protocols include single-agent use of L-

asparaginase (Elspar; 10,000-40,000 IU/m<sup>2</sup> IM once every 2-3 weeks) or cyclophosphamide (as described previously) and combinations of either cytosine arabinoside or cyclophosphamide with prednisone.

Unfortunately, the likelihood that remission rates and survival times for specific chemotherapeutic protocols and well characterized lymphoid neoplasms in horses (based on a suitably large number of cases) will soon be available is not high. Nevertheless, anecdotal reports suggest remission is possible in some cases of equine lymphoma.

### PLASMA CELL MYELOMA

Plasma cells are terminally differentiated B cell lymphocytes. Malignant transformation can result in three categories of tumors: chronic B cell lymphocytic leukemia, B cell lymphoma (considered above), and plasma cell tumors. Plasma cell tumors occur rarely in the horse; most of the reported information is derived from individual cases and a retrospective series of 10 cases (Edwards et al, 1993; see readings list). No risk factors have been established, and affected animals have ranged from 3 months to 22 years of age. *Solitary plasmacytoma* is the term used for a single extramedullary tumor. However, the most common form of plasma cell tumors in horses involves the bone marrow and is called *multiple myeloma*.

### Clinical Signs

Clinical signs are associated with the sites of tumor invasion and include limb edema, ataxia, lameness, epistaxis, lymphadenopathy, weight loss, and anorexia. Secondary infections that commonly involve the lower respiratory or urinary tract may develop. Anemia and hyperglobulinemia are the most common abnormal laboratory findings. With myelophthisic disease, the anemia may be severe and accompanied by leukopenia and thrombocytopenia. Hypoalbuminemia may accompany hyperglobulinemia. A monoclonal gammopathy is detected in nearly all cases by serum electrophoresis and reflects the malignant transformation and clonal expansion of a single plasma cell lineage. The monoclonal protein, called a *paraprotein*, may be a complete or partial immunoglobulin, the majority of which are in the IgG class. Analysis of urine may reveal proteinuria, and the heat-precipitation method has confirmed the presence of light chains (Bence Jones protein) in the urine of a few horses. Occasionally, hypercalcemia may be found as a paraneoplastic condition.

### Diagnosis

In human patients, definitive diagnosis is based on the demonstration of bone marrow plasmacytosis (>10% of cells) or an extramedullary plasmacytoma and one of the following: (1) a serum monoclonal gammopathy; (2) detection of a urine monoclonal protein; or (3) osteolytic lesions. The majority of equine cases have a monoclonal gammopathy; however, cases in which the serum globulin content was within normal limits have been described. Further examinations should include skeletal survey radiographs of the long bones and cervical vertebrae and biochemical tests to detect renal or hepatic involvement.

### Prognosis and Treatment

Most horses die or are euthanized within 4 months of developing clinical signs, but longer survival times have been reported in a few horses treated with antineoplastic agents. Melphalan (Alkeran), prednisone, and cyclophosphamide have been used in the treatment of multiple myeloma in an 18-year-old Quarter Horse mare. Diagnosis was confirmed 1 week before foaling. Chemotherapy was started after the foal was weaned at 4 days of age; however, dosages were not reported, and plasmapheresis was also performed. The mare was euthanized 7 months after diagnosis because of severe chronic laminitis. A 20-year-old horse with multiple myeloma was also treated with melphalan (7 mg/m<sup>2</sup> PO q24h for 5 days, and then every 3 weeks). The horse's condition remained stable for 1 year after diagnosis.

### MYELOID LEUKEMIAS

Myeloproliferative disorders are characterized by medullary and extramedullary proliferation of bone marrow constituents, including the erythroid, granulocytic, monocytic, and megakaryocytic cell series. Myelodysplastic syndromes are characterized by refractory cytopenia, which generally progresses to acute myeloid leukemia. Classification schemes for myeloid leukemia are based on the degree of differentiation of the transformed cell line. For example, chronic myeloid leukemia involves neutrophils and late precursor cells, whereas acute myeloid leukemia involves myeloblast cells. In general, chronic leukemias are less aggressive than acute leukemias. Reports of myeloproliferative disorders of horses are rare and are dominated by acute leukemias of the granulocytic cell series.

### Clinical Signs

In a review of 11 reported cases of myelogenous leukemia in the horse, the ages ranged from 10 months to 16 years, and both genders and various breeds were affected. Common clinical findings included ventral and peripheral edema, petechiae, weight loss, depression, and enlarged lymph nodes. Less common findings were fever, epistaxis, pneumonia, exercise intolerance, and colic. All were found to be anemic and thrombocytopenic and had circulating neoplastic cells; the majority had neutropenia and a gam-mopathy. Secondary infections seem more common in this

form of hematopoietic disorders, presumably as a result of immunosuppression. Two horses with myelomonocytic leukemia developed pulmonary aspergillosis.

### Diagnosis

Bone marrow examination confirms the diagnosis. Confirmation of cell lineage may be morphologically obvious. When needed, further characterization is possible with histochemical and immunohistologic or flow cytometric identification of cell-surface antigens or enzyme content.

### Prognosis and Therapy

Myelogenous leukemias are notoriously resistant to common antineoplastic agents. However, chemotherapy has been attempted in at least two cases of equine acute myelomonocytic leukemia. These horses were given cytosine arabinoside, based on a low-dose protocol (10 mg/m<sup>2</sup> q12h for 3 weeks) adopted from human cancer medicine. The aim of this therapy is to promote terminal differentiation of the neoplastic cell line and diminish clonal expansion. Newer modalities are being tested in human patients and include the use of hematopoietic cytokines and bone marrow transplantation, but no reports of similar use in equine cancer patients exist.

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## CHAPTER 6.10

# Vasculitis

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**V**asculitis, an inflammation and necrosis of blood vessel walls, can affect any size, location, or type of vessel in any age, breed, or sex of horses. The most commonly recognized cause, often called *purpura hemorrhagica*, is immune-mediated vasculitis secondary to respiratory infection. However, any infection, neoplasm, or drug may serve as the source of antigen. Vasculitis is not always primarily immune-mediated and may also occur with equine viral arteritis, endotoxemia, septicemia, and photoactivated vasculitis. The etiology of some cases, however, remains undetermined, despite careful examination for the focus of antigenic stimulation.

The mechanism of tissue damage in immune-mediated vasculitis is thought to be caused by a type III hypersensitivity reaction in which soluble immune complexes are deposited in blood vessel walls in areas of increased vascular permeability. Activation of complement by immune complexes releases complement components and other compounds that are chemotactic for neutrophils. Proteolytic enzymes released by infiltrative neutrophils directly damage vessel walls. Subsequent compromise of the vessel lumen results in edema, hemorrhage, and ischemic changes in the tissues supplied or drained by the affected vessels.

### ETIOLOGY

#### Purpura Hemorrhagica

Purpura hemorrhagica is an acute, probably immune-mediated, necrotizing neutrophilic leukocytoclastic vasculitis that is most commonly a sequela to infection with *Streptococcus equi*, although it may also occur following infection with other streptococcal species, *Rhodococcus equi*, influenza, equine herpes virus I, and, more rarely, other chronic bacterial or viral infections. If the clinical presentation is mild, signs include edema of the distal extremities with or without a few petechiae on mucous membranes. Severe cases are characterized by extreme edema, numerous petechiae and ecchymoses, fever, tachycardia, tachypnea, anorexia, and rapid weight loss. Edema subsequent to fibrinoid necrosis of blood vessels in the pulmonary and gastrointestinal system may result in severe respiratory distress and colic.

Most cases of purpura hemorrhagica occur following acute *S. equi* infections (strangles) 2 to 4 weeks after the onset of clinical signs. Purpura also occurs in horses with occult *S. equi* infections without clinical signs, in horses with aberrant *S. equi* abscesses, in horses previously sensitized and reexposed to the organism, and occasionally in

horses after vaccination for *S. equi*. Culture of the nasopharynx or guttural pouches may yield *S. equi* in horses with occult infections and in horses recovered from acute infection, as they continue to shed the organism for 3 to 6 weeks after clinical recovery.

Horses with purpura hemorrhagica secondary to *S. equi* infections have stronger antibody responses to streptococcal proteins than horses infected and recovered from *S. equi* that do not develop purpura. Affected horses have high plasma concentrations of C3 and circulating immune complexes of IgA to M proteins of *S. equi*. In one report, two horses with purpura had a marked reduction in IgG specific for *S. equi* during the acute stage of purpura, which subsequently increased during the recovery phase, thus suggesting that immune complex depletion had occurred during the acute phase. These findings strongly support an immune-mediated mechanism for the vasculitis.

#### Equine Infectious Anemia and Equine Ehrlichiosis

See Chapter 6.4: "Hemolytic Anemia."

#### Equine Viral Arteritis

Equine viral arteritis (EVA) is an RNA virus in the genus *Arterivirus* that is widely distributed in horses throughout the world, although the prevalence varies widely between countries and within breeds. Serologic studies of horse populations indicate that most infections with EVA are subclinical or inapparent. Systemic clinical disease resembles other respiratory viral infections in the horse and it is possible that some clinical cases of EVA are unrecognized in undifferentiated cases or outbreaks of respiratory disease. Most clinically apparent cases of EVA occur in young, old, or debilitated horses with compromised immune systems.

Mares infected venereally by acute or chronically infected stallions may abort in the late acute phase or early in the convalescent stage of infection, irrespective of the presence or absence of clinical disease.

Aerosol transmission studies indicate the initial multiplication of virus takes place in bronchial macrophages followed by viremia and dissemination to the small arteries and, to a lesser extent, venules throughout the body. Infection of the endothelial cells of the intima results in fibrinoid necrosis with lymphocytic infiltration of the tunica media followed by edema and lymphocytic infiltration of the adventitia. Thrombosis in affected vessels is rare and, when present, usually occurs in the lung and intestinal tract.

The most consistent clinical signs seen in EVA are pyrexia and a lymphocytic leukopenia. Distal limb edema with a stiff gait, conjunctivitis, and rhinitis are also frequent clinical findings. A maculopapular or urticarial rash, particularly of the neck and thorax, may also be seen. In more severe cases, respiratory distress and more extensive dermal and subcutaneous edema that extends to the ventral midline and face may be present.

Diagnosis of EVA can be made by serologic evaluation of paired acute and convalescent serum samples taken 21 to 28 days apart. Virus isolation may be performed early in the disease process by culturing nasopharyngeal swabs or washings or by culturing the buffy coat of blood. Specimens collected from the nasal passage should be placed in appropriate viral transport media immediately after collection; blood collected in citrate, heparin, or EDTA is suitable for virus isolation from the buffy coat. Alternatively, immunoperoxidase testing of skin biopsies, particularly from areas of edema or maculopapular eruptions, may demonstrate the virus.

### Photoactivated Vasculitis

Photoactivated vasculitis is an uncommon disease that affects mature horses during the summer months in regions with strong solar radiation. Lesions are limited to the non-pigmented portion of the lower extremities. Affected limbs are edematous and painful, with variable erythema, serum exudation, and crusting. Histologic evaluation of skin biopsies reveals degenerative changes of the walls of superficial dermal blood vessels with variable thrombosis and a mixed inflammatory infiltrate. Direct immunofluorescence testing may demonstrate the deposition of IgG and C3 in the walls of affected vessels; however, whether the response is truly immunologic or is a nonspecific response of porphyria is unknown.

### CLINICAL SIGNS OF VASCULITIS

The predominant clinical sign is edema of the skin and subcutaneous tissue and is most often present in the distal extremities, face, and ventral abdomen. Facial edema may be confined to the muzzle, periorbital area, or the pinnae. In more severely affected cases, edema may extend into the proximal extremities and cause pharyngeal swelling that results in respiratory stridor. Wheals and larger confluent areas of edema may occasionally be present on the body. The edematous areas are sharply demarcated, pitting, warm, and painful. Serum leakage, purpura (extravasation of RBCs into surrounding tissue), and crusting may occur. In more severe cases, necrosis of affected areas results in ulceration and/or sloughing of the skin, particularly in the distal limbs. Mucous membranes and sclerae are often hyperemic and have multiple petechiae and ecchymoses. Less commonly, bullae and ulcerations occur on mucous membranes.

Although lesions of the skin predominate, any organ may be affected and result in a constellation of clinical signs. Lesions in muscles and joints contribute to generalized soreness and reluctance to move and, in severe cases, may resemble rhabdomyolysis. Lesions within the gastrointestinal tract and respiratory and neurologic systems may result in colic, respiratory distress, and neurologic

deficits, respectively. Tachycardia, tachypnea, fever, depression, anorexia, and weight loss are common in severe cases and may be related to the underlying disease process.

### DIAGNOSIS

Definitive diagnosis is made from the history, clinical signs, and skin biopsy results. Six- to 8-mm full-thickness punch biopsies of the skin should be obtained from the most recently affected areas and preserved in 10% buffered neutral formalin and Michel's transport media. Multiple biopsies from several sites are often necessary to find definitive lesions. The hallmark histopathologic findings of hypersensitivity vasculitis are infiltration of neutrophils, the presence of neutrophil nuclear debris (leukocytoclasia), and fibrinoid necrosis of affected dermal vessels. Neutrophilic inflammation is present early in the disease process; biopsies of more chronic lesions may have mixed infiltrates that consist of lymphocytes, macrophage, and/or eosinophils. When the inflammatory cells in and around dermal vessels consist primarily of lymphocytes, viral injury to the vessels should be ruled out. Immunoperoxidase staining for equine herpesvirus 1 and equine viral arteritis may provide an etiologic diagnosis in these cases.

Direct immunofluorescence tests of biopsies preserved in Michel's media may demonstrate immunoglobulin and complement deposition in and around vessel walls. Inflammatory cells rapidly phagocytize immunoglobulin complexes, and positive tests are usually only found in biopsies from lesions 4 to 24 hours old. A few reports of vasculitis have found low antinuclear antibody (ANA) titers (1:10-1:40) in affected horses; however, the significance of these findings is unknown. Positive ANA titers may be found in other immune-mediated diseases as well as in some normal horses.

Hematologic and serum biochemistry findings are nonspecific and depend on the primary disease and the severity and number of body systems affected. Approximately 60% of horses will have one or more findings of chronic inflammatory disease consisting of neutrophilic leukocytosis, hyperfibrinogenemia, hypergammaglobulinemia, and mild to moderate anemia. The clotting profile and platelet count are usually normal, which helps differentiate cases with petechiae and ecchymoses from consumptive coagulopathy and immune-mediated thrombocytopenia, although vasculitis may rarely be associated with both of these conditions. Horses that exhibit myalgia may have a moderately to marked increase in serum creatine phosphokinase and aspartate aminotransferase activities. Horses with renal lesions may have increased serum creatinine concentration, proteinuria, and trace to microscopic hematuria.

Because most cases of equine cutaneous vasculitis are secondary to a primary disease process, a detailed examination and a complete set of diagnostic procedures should be performed to discover the inciting cause or rule out other disease processes (see Etiology).

### TREATMENT

Treatment of purpura hemorrhagica and similar idiopathic vasculitides consists of the following: (1) removing the

antigenic stimulus; (2) suppressing the immune response; (3) reducing vessel wall inflammation; and (4) providing supportive care. Any drugs given when the clinical signs occurred should be discontinued, or, if continued medication is necessary, an alternate drug should be chosen from a chemically unrelated class. A thorough examination should be performed to identify a primary disease process. Any bacterial pathogens should be cultured and an *in vitro* sensitivity performed. Because most cases of purpura hemorrhagica are a sequela of *S. equi* infection, penicillin (procaine penicillin G 22,000-44,000 U/kg IM q12h or sodium or potassium penicillin 22,000-44,000 U/kg IV q6h) should be administered for a minimum of 2 weeks unless specifically contraindicated. Any accessible abscess should be drained. If gram-negative bacteria are suspected or isolated, additional appropriate antimicrobial therapy should be used. Antimicrobial therapy is also indicated to limit or prevent secondary septic complications such as cellulitis, tenosynovitis, arthritis, pneumonia, and thrombophlebitis.

Systemic glucocorticoids are warranted because purpura hemorrhagica and other undefined vasculitides are most likely immune-mediated. In addition, systemic glucocorticoids reduce inflammation of the affected vessel walls and subsequent edema formation. Dexamethasone (0.05-0.2 mg/kg IM or IV q24h) or prednisolone (0.5-1.0 mg/kg IM or IV q24h) may be used; however, clinical experience indicates that dexamethasone is more effective during initial therapy. The minimum dose that provides a decrease in clinical signs should be used. After substantial reduction and stabilization of clinical signs, the dose of glucocorticoids may be decreased by 10% per day over 10 to 21 days. When the dose of dexamethasone is 0.01 to 0.04 mg/kg per day, it may be given orally; alternatively, prednisolone may be substituted at ten times the dexamethasone dose. The bioavailability of oral prednisolone is 50%; thus an effective parenteral dose administered orally may result in relapse of clinical signs. Prednisone is poorly absorbed from the gastrointestinal tract and is not detectable in the blood of most horses after oral administration; thus its use is not recommended. Hydrotherapy, application of pressure bandages, and hand-walking should be used to decrease or prevent edema. Furosemide (1 mg/kg IV q12h) may help reduce edema in severe cases. A tracheostomy may be indicated if respiratory stridor is present from edema of the nasal passages, pharynx, and/or larynx. Dysphagic horses should be supported with intravenous or nasogastric administration of fluids. Nutritional support may be necessary in horses with prolonged dysphagia. Nonsteroidal antiinflammatory drugs (flunixin meglumine 1.1 mg/kg IV, IM or PO q12h or phenylbutazone 2.2-4.4 mg/kg IV or PO q12h) are indicated to provide analgesia in horses with lameness, colic, myalgia, or other painful conditions. NSAIDs may also help reduce the inflammation in affected vessel walls.

Horses with EVA do not require specific therapy because the majority of cases recover uneventfully. Glucocorticoids are contraindicated because vessel wall damage results from direct viral injury. Occasionally horses with severe clinical signs of lower respiratory disease will need antimicrobial therapy to prevent or treat secondary bacterial pneumonia. Horses with EIA are infected for life. Glucocorticoids are contraindicated because they may result in increased viral replication and occurrence of clinical disease. Horses with equine ehrlichiosis may benefit from glucocorticoid therapy; however, they should be treated with oxytetracycline to eliminate the organism (see Chapter 2.12: "Equine Monocytic Ehrlichiosis" and Chapter 6.4: "Hemolytic Anemia"). Horses with photoactivated vasculitis should be stabled during daylight hours to prevent any further exposure to sunlight. The vascular inflammation should be treated with systemic glucocorticoids in a regimen similar to that for purpura hemorrhagica. Topical applications of glucocorticoids with or without antibiotics are not effective. Irritating topical solutions should not be used.

## PROGNOSIS

With early and vigorous treatment, the prognosis of purpura and other similar vasculitides is fair, particularly when the antigenic stimulus can be identified and removed. Most cases resolve in less than one month; however, horses that present with hypergammaglobinemia often require 4 to 8 weeks of glucocorticoid treatment. Some cases, particularly those in which an inciting antigenic stimulus cannot be identified, relapse repetitively in the absence of continuous steroid therapy. Secondary complications from necrosis and skin slough—such as cellulitis, tenosynovitis, septic arthritis, laminitis, and chronic granulation tissue—may prolong recovery and limit the future athletic use of the horse. In severe peracute cases (anaphylactoid purpura), large confluent areas of necrosis and hemorrhage in the gastrointestinal tract and/or the lungs can result in rapid death. As many as 30% of cases have been reported to die or are euthanized because of serious sequellae. Most cases of photoactivated vasculitis respond favorably to treatment.

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# SECTION VII

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## Upper Airway Diseases

*Edited by Dr. Eric J. Parente*

### CHAPTER 7.1

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## Endoscopic Evaluation of the Upper Respiratory Tract

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Endoscopy is the primary diagnostic tool for evaluation of the upper respiratory tract. Although some functional abnormalities of the larynx or pharynx cannot be discerned during examination of a standing horse, if the examination is performed appropriately many of these abnormalities can be spotted. Almost all of the structural abnormalities of the arytenoids, epiglottis, or nasal passage can be easily identified during examination of the resting horse.

To determine a diagnosis, the endoscopic findings should always be considered in conjunction with the historic information (including history of respiratory noise), and the physical examination of the respiratory tract. The external examination is too often overlooked. The examination should include palpation of the trachea, visual assessment for facial deformity and nasal discharge, determination of airflow through each nostril, palpation of the alar pouch/folds, and palpation of the muscular processes of the arytenoids/throat latch region.

### EQUIPMENT

Many quality flexible fiberoptic and video endoscopes are commercially available. Video endoscopes provide superior image quality and because the image is projected onto a monitor, more than one viewer can see the lesion. However, because of its size video equipment is difficult to use under field conditions. Most fiberoptic endoscopes provide a good image, but quality can suffer from disruption of the optic or light fibers. A 300-W xenon light source is required to provide adequate lighting for video endoscopes, whereas a 150-W halogen light source is adequate for fiberoptic endoscopy. To complete most examinations easily, the diameter of the endoscope should be less than 12 mm for adults and less than 9 mm for younger animals.

### EXAMINATION OF THE RESTING HORSE

To ensure that an examination is comprehensive and performed efficiently, it is always best to develop a standard routine. Although some practitioners perform the examination with just themselves and one other person holding the horse, it is beneficial to have a third person pass the endoscope for greater control of the instrument in the nasal passage. The presence of a third person allows the examiner to use both hands to direct the endoscope. A twitch for restraint is always recommended for greater control over the horse's head position, and no sedatives should be given that would falsely alter the functional assessment of the upper airway.

Passage of the endoscope into the nasal passage should be done quickly for the first few centimeters, and the endoscope should be directed ventral and medial to ensure it slides down the ventral meatus. Horses will object the most when the endoscope is first passed, therefore it is easier for the examiner to pass the endoscope quickly through the rostral part, evaluate the caudal part of the upper airway, and then evaluate the rostral nasal passage while retracting the endoscope instead of during insertion.

### Epiglottis

The examination typically begins when the endoscope is just rostral to the larynx—in an adult, approximately 35 cm from the tip of the nose. An overall assessment should be made of the pharyngeal vault. Depending on the horse's age, a varied amount of lymphoid hyperplasia will be present. It is common for the younger horse to have more lymphoid hyperplasia, but this condition has not been correlated with any specific dysfunctions. The epiglottis should be positioned dorsal to the palate and have a distinctly

"serrated" edge with a clear vascular pattern. This pattern may not be seen in cases of epiglottitis or epiglottic entrapment. Although entrapment of the epiglottis with the subepiglottic tissues will obscure visualization of the dorsal surface of the epiglottis, a clear margin of the entrapping membrane should be seen. This condition is very different from cases of epiglottitis in which swelling of the epiglottic and subepiglottic tissues is present but no entrapment of the epiglottis by membrane exists. In both cases the epiglottis remains dorsal to the palate; these conditions should not be confused with dorsal displacement of the soft palate. Infrequently entrapment and dorsal displacement of the soft palate can occur simultaneously. Because only the displaced palate is visible through the endoscope that has been passed via the nasal passage, this diagnosis can only be confirmed with a lateral radiograph or endoscopic examination through the mouth while the horse is under general anesthesia. The examiner should suspect a concurrent entrapment with a dorsal displacement when the horse demonstrates no neurologic deficits or dysphagia associated with the persistent displacement (Figure 7.1-1).

The apparent stiffness of the epiglottis is greatly influenced by its position within the pharynx and the pull of the hyoepiglotticus muscle. If the horse is very relaxed and breathing normally, the epiglottis should have a convex shape and stand off of the palate. If the horse is stressed and breathing with increased effort, the epiglottis will often appear to sit further back in the pharynx and may have a flat or more concave shape. The horse may even displace its soft palate more easily, but this displacement should not be overinterpreted as abnormal, particularly in the younger horse.



**Figure 7.1-1** Persistent displacement of the soft palate with concurrent entrapment of the epiglottis. With concurrent entrapment, the contour of the epiglottis is sometimes evident in the palate.

## Larynx and Pharynx

The arytenoids should be evaluated for their overall appearance and symmetry. Disruption of the corniculate mucosa, or areas of granulation tissue on the axial surface may be indicative of an early chondrosis. The movement of the arytenoids should initially be assessed with the horse at rest and later in the examination during nasal occlusion and after swallowing.

Close attention should also be paid to the vocal chords and the ventricles of the larynx. Because laser ablation/resection of the cord or ventricle has become more commonplace for the treatment of hemiplegia, an abnormal appearance of these structures may be a clue to a previous problem and treatment. Depending on how the previous procedure was performed, all that may be noticed is a loss of normal mucosa and a scarred appearance without complete absence of the cord (Figure 7.1-2).

After the initial evaluation of the structures in the laryngeal region has taken place, certain maneuvers should be performed to assess the function of the larynx and pharynx. To evaluate pharyngeal function, the endoscope should be passed into the trachea. Horses frequently cough during this procedure, but no feed material should be evident within the trachea when the endoscope is initially passed. If a possibility exists of prior severe respiratory problems or respiratory surgery, the ventral aspect of the trachea should be observed for a tracheotomy scar. Tracheotomy scars are often difficult to discern externally, but are easily observed within the trachea as a larger circular stellate lesion. When the endoscope is withdrawn from the trachea the soft palate is frequently displaced. The horse should swallow quickly and put the palate into its normal position on the first attempt. Often the swallow takes place



**Figure 7.1-2** Scarring of both vocal cords is evident and is the result of incomplete noncontact laser ablation of the cords.

just as the endoscope comes out of the larynx so that the free edge of the palate is never observed. The examiner should make the horse swallow by stimulating the pharynx with water from the endoscope or bumping the pharyngeal wall with the endoscope. Abnormalities of pharyngeal function or abnormalities below the epiglottis, such as a cyst, may manifest themselves. In a horse with normal pharyngeal function, the epiglottis should always be above the palate after swallowing. Observation of the pharynx during nasal occlusion is also helpful. It is normal for horses to have air escape around the aryepiglottic folds during prolonged nasal occlusion. Some mild to moderate degree of dorsal pharyngeal collapse during nasal occlusion is also normal. Most horses will maintain the epiglottis above the palate; horses that displace their palates very easily are more likely to displace during very strenuous activity, but there is not a direct correlation.

The larynx is also evaluated during these maneuvers of swallowing and nasal occlusion. Full symmetric abduction of the arytenoids is achieved very quickly immediately after swallowing, and can be used to assess the grade of hemiplegia. The degree of arytenoid abduction can also be assessed during nasal occlusion, but this does not create the same level of abduction unless the horse is occluded for a substantial amount of time. Asynchronous movement of the arytenoids with full symmetric vocal fold abduction during swallowing (grade II hemiplegia) is more common than synchronous movement coupled with symmetric abduction (grade I). Both grades should not suffer any degree of obstruction during exercise and are considered normal. Horses that cannot achieve full abduction of one arytenoid may suffer respiratory compromise during exercise, depending on its intensity.

### Other Structures

Once a full assessment of the horse's larynx and pharynx is completed, other structures of the upper airway can be



**Figure 7.1-3** Normal appearance of ethmoid turbinates.

evaluated while the endoscope is slowly withdrawn. There is significant variability to the dorsal pharyngeal recess, but this is rarely the location of abnormalities. The guttural pouch openings should be clear of any discharge. Discharge that does not come from within the guttural pouch is infrequently observed at the openings. The pouches should be evaluated by internal inspection if there is any question about the source of nasal discharge. To do so, a biopsy instrument can be placed through the biopsy channel of the endoscope and into the guttural pouch as a lead. The endoscope is rotated so the biopsy instrument pries the guttural pouch flap open as the endoscope is advanced into the pouch. The examiner can easily evaluate both pouches without moving the endoscope to the other nasal passage. A small amount of sedation to facilitate performance of this procedure is beneficial.

The remainder of the nasal passage should be evaluated for abnormal swellings, masses, or sources of discharge. The ethmoid turbinates normally appear bulbous (Figure 7.1-3), and the middle meatus should be observed for discharge through the nasomaxillary opening. The dorsal and ventral turbinates should not have direct contact with the septum at any location. It is often difficult to discern small deviations and swellings in this region because of the small area visible through the endoscope. The other nasal passage should be examined in a similar fashion and can often be used as a normal control for comparison. If a nasal passage problem is initially suspected, it is probably better to start the examination with the normal side and complete the evaluation of the larynx and pharynx before proceeding to the abnormal side.

A functional abnormality is often suspected because of exercise intolerance or abnormal respiratory noise during exercise. A thorough endoscopic examination of the resting animal may elucidate the problem, but some abnormalities are not evident unless the horse is placed under the much greater respiratory demands of hard exercise. Endoscopic examination immediately after the horse has exercised can be misleading. Even normal horses naturally have a much more flaccid looking throat and displace their palates more easily when first pulling up after exercise. The same muscles that maintain structural integrity of the respiratory lumen relax just like all skeletal muscles relax at the conclusion of strenuous exercise. Therefore a conclusion about the functional stability of the airway may be inaccurate when the horse is evaluated in a fatigued, relaxed condition.

### ENDOSCOPY OF THE EXERCISING HORSE

Endoscopy of the horse while it is exercised on a high-speed treadmill may be necessary if a high degree of suspicion exists of an upper respiratory abnormality but no abnormality can be detected during examination at rest. Many abnormalities can cause significant respiratory compromise during strenuous exercise that cannot be determined on resting endoscopic examination. These include forms of pharyngeal collapse, axial deviation of the aryepiglottic folds, epiglottic retroversion, and intermittent epiglottic entrapment/dorsal displacement of the soft palate.



Endoscopy during exercise needs to be performed at a referral practice that has the capabilities for performing such an examination. For safety reasons and the diagnostic value of the test, the team of individuals performing the examination must be experienced. Although endoscopy during exercise may be beneficial in many problems that cannot be discerned during endoscopy of the resting horse, it is not always the final answer. Many of the upper respiratory problems are dynamic, and if all the same conditions of speed, head/neck flexion, and fatigue are not reproduced, a false negative is likely to result. Of the known upper respiratory abnormalities, dorsal displacement of the soft palate is the most likely condition that will not be re-

produced on a high-speed treadmill despite consistent problems under true competition.

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## CHAPTER 7.2

# Diagnosis of Sinus Diseases

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**D**iagnosis and treatment of diseases of the paranasal sinuses and conchae of horses is complicated by the large size of these structures, their complex anatomy, the difficulty of gaining access to them, and the advanced state of many diseases before diagnosis is made.

The largest paranasal sinus, the maxillary sinus, is divided into caudal and rostral parts by a thin septum located anywhere from the middle of the first molar to the middle of the third molar. The frontal sinus has a large communication at its rostral end with the dorsal conchal sinus and combines with the dorsal conchal sinus to form the conchofrontal sinus. The ventral conchal sinus communicates with the rostral maxillary sinus over the infraorbital canal and is separated from the caudal maxillary sinus by a thin sheet of bone, the caudal bulla of the ventral conchal sinus. The caudal bulla of the ventral conchal sinus attaches ventrally to the septum that divides the maxillary sinuses and combines with it to form the rostral wall of the caudal maxillary sinus. The conchae are delicate scrolls of bone that are attached laterally in the nasal passage and contain the conchal sinuses. The caudal and rostral maxillary sinuses have separate openings into the middle nasal meatus, and the caudal maxillary sinus communicates with the frontal sinus through the large frontomaxillary opening. The opening from the caudal maxillary sinus is a transverse slit between the rostral edge of the frontomaxillary opening and the caudal bulla of the ventral conchal sinus. The opening from the rostral maxillary sinus is in the lateral and dorsal aspect of the sinus. Diseases that originate in one sinus cavity may well extend into others through bone destruction or displacement.

### CLINICAL DIAGNOSIS OF SINUS DISEASE

Most sinus diseases cause a unilateral mucopurulent nasal discharge unless inflammation occludes the nasomaxillary opening so that fluid is retained in the sinuses. A bilateral discharge is rare in unilateral cases, because the source of fluid is usually rostral to the most caudal end of the nasal septum, a feature that can help distinguish between diseases of the sinuses and those of the guttural pouches, lungs, and pharynx. Blood-stained nasal discharge may be evident in horses with ethmoid hematoma, tumors, or fungal infections. In long-standing cases, unilateral facial swelling is evident in the maxilla. Swelling is usually more severe in young horses. Diseases of the sinuses can cause abnormal respiratory noise from impingement of medial walls of the conchae into the nasal passage, displacement of the nasal septum, or by extension of sinus masses into the nasal passage and pharynx. Exophthalmos may be seen in cases of fungal granuloma and neoplasia, and epiphora can develop in some diseases by compression of the osseous nasolacrimal duct.

Percussion can be used to detect fluid or space-occupying masses within the sinuses, but this method is not always reliable. To percuss the sinuses, the clinician taps the fingers of one hand sharply against the overlying bones; the corresponding area on the normal side is percussed immediately afterwards for comparison. If the horse's mouth is held open simultaneously, resonance increases and abnormalities are easier to detect. An oral examination should be performed to detect dental abnormalities. Changes in peripheral blood samples are uncommon, except that the packed cell volume may be decreased in horses with chronic infections or neoplasia.

Endoscopy during exercise needs to be performed at a referral practice that has the capabilities for performing such an examination. For safety reasons and the diagnostic value of the test, the team of individuals performing the examination must be experienced. Although endoscopy during exercise may be beneficial in many problems that cannot be discerned during endoscopy of the resting horse, it is not always the final answer. Many of the upper respiratory problems are dynamic, and if all the same conditions of speed, head/neck flexion, and fatigue are not reproduced, a false negative is likely to result. Of the known upper respiratory abnormalities, dorsal displacement of the soft palate is the most likely condition that will not be re-

produced on a high-speed treadmill despite consistent problems under true competition.

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## CHAPTER 7.2

# Diagnosis of Sinus Diseases

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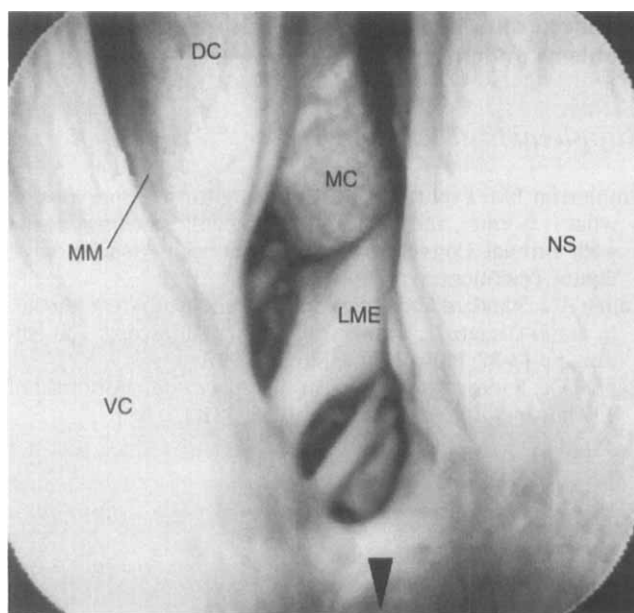
**D**iagnosis and treatment of diseases of the paranasal sinuses and conchae of horses is complicated by the large size of these structures, their complex anatomy, the difficulty of gaining access to them, and the advanced state of many diseases before diagnosis is made.

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**Figure 7.2-1** Endoscopic view of the caudal end or fundus of the right nasal passage, demonstrating the middle concha (MC), the lateral masses of the ethmoid labyrinth (LME), which with the middle concha forms the ethmoturbinates, the nasal septum (NS), dorsal concha (DC), the ventral concha (VC), and middle meatus (MM). The arrowhead points towards the pharynx. This view reveals lesions from the sinuses and sinus fluid draining from the nasomaxillary opening and into the middle meatus. Variations in size and shape of the middle concha should not be confused with a mass in this area.

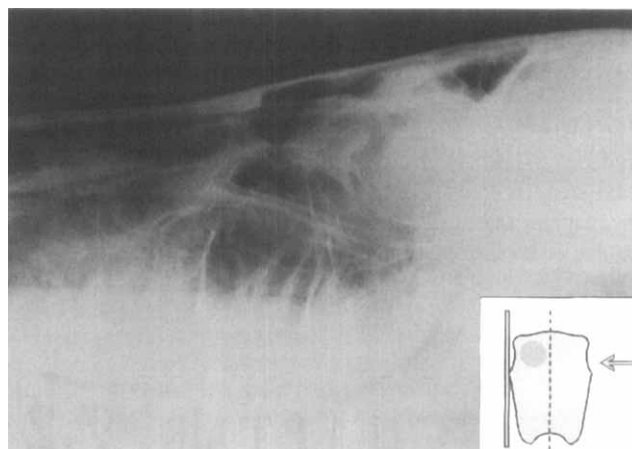
### Endoscopy of the Nasal Passages

Endoscopy is used to detect sinus abnormalities that extend into the nasal passages and to rule out other diseases of the upper respiratory tract and guttural pouches that can present with similar clinical signs. The clinician must pay special attention to the ethmoturbinates and the caudal end of the middle meatus (Figure 7.2-1) because blood, pus, and masses can be seen at these sites in horses with sinus disease.

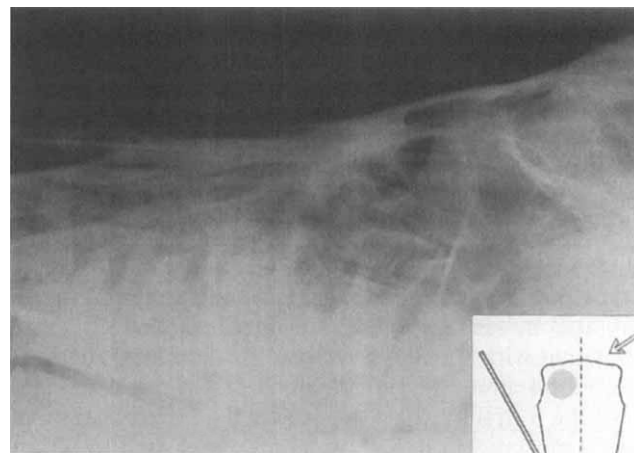
### Radiography

Despite the large mass of the equine skull, diagnostic quality radiographs of the sinuses are possible with a portable x-ray tube, because bone overlying the sinuses is thin and the amount of air within them acts as a natural contrast agent for soft tissue densities and fluid (Figure 7.2-2). Standard projections are lateral (see Figure 7.2-2), lateral oblique (Figure 7.2-3), and dorsoventral. Recommended settings for lateral or lateral oblique radiographs of the equine skull are 80 kVp, and 10 mA for 0.1 seconds or 20 mA for 0.06 seconds. For the dorsoventral projection, 80 kVp and 10 mA for 0.13 to 0.4 seconds or 20 mA for 0.16 to 0.2 seconds are recommended.

Radiographs of sinus and dental diseases can be difficult to interpret, and angles of projection and exposure factors must be selected carefully to span the wide range of radiodensities from thin plates of bone to dense enamel, all adjacent to radiolucent air spaces. Therefore an imag-



**Figure 7.2-2** Lateral radiographic view of the sinuses of a horse with a diffuse mass caused by a fungal granuloma in the right paranasal sinuses. Inset shows position of the plate relative to the sinus mass (*shaded*), sagittal plane of the head (*broken line*), and x-ray beam (*arrow*).



**Figure 7.2-3** A 30-degree oblique radiographic view of the sinuses of the same horse as that pictured in Figure 7.2-2. Inset shows position of the plate relative to the sinus mass (*shaded*), sagittal plane of the head (*broken line*), and x-ray beam (*arrow*).

ing system with a wide range of exposure latitude and photographic contrast is desirable. Although the high-speed versions of traditional calcium tungstate intensifying screens are generally satisfactory for equine dental radiographs, salts of rare-earth metals, or phosphors, increase light emission; relatively low exposure times are used. Rare-earth screens are now available in a wide range of speeds and detail, and medium-speed and medium-detail screens are useful for most equine dental radiographs. Grids are rarely needed for equine dental radiography, because the amount of scattered radiation is relatively small.

Grids are not recommended in standing animals, because exposure must be increased and alignment for oblique projections is difficult.

Lateral radiographs of the skull are diagnostic for many diseases, but limitations arise from image distortion caused by beam divergence, magnification, and superimposition. Occasionally, removal of fluid from sinuses allows more complete assessment of lesions obscured by fluid lines. Accuracy of head positioning for lateral radiographs can be assessed by checking that the premaxillary borders of the nasomaxillary notch are close together and parallel with each other.

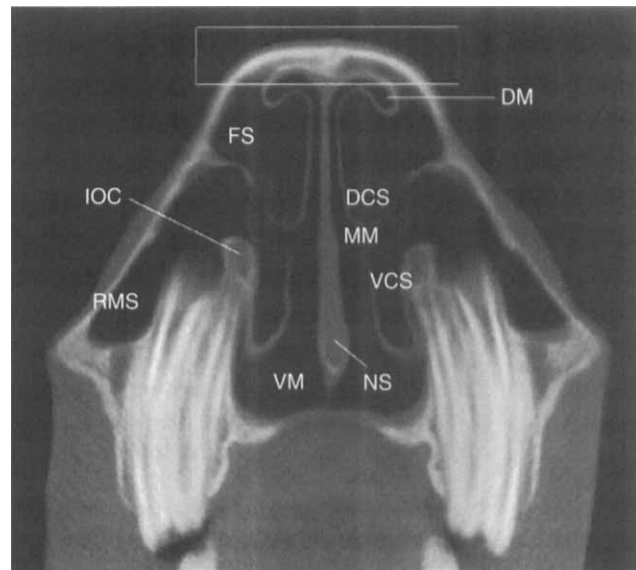
To improve views of tooth roots, the cassette can be held at an angle beneath the jaw on the affected side and the beam directed obliquely approximately 60 degrees in a dorsal to ventral direction. Thick or inspissated pus in the ventral conchal sinus can be obscured by tooth roots on lateral views but might be evident on dorsoventral projections. Sinus cavities are difficult to evaluate on dorsoventral views because the cheek teeth and the overlying masseter muscles obscure much of the field. However, this view does demonstrate the septum and any effect sinus disease has on its position. The ventrodorsal projection with offset mandible can be used to demonstrate low-grade periapical infection, alveolar disease, and chronic osteitis, if standard oblique radiographs yield inconclusive findings.

### Computed Tomography

In computed tomography (CT), computer-controlled processes enhance the information obtained by absorption of the x-ray beam by the individual structures through which the beam is passed. Radiographic images of transverse sections can be obtained at selected intervals. The major advantage of CT over conventional radiographs is elimination of superimposition artifacts and enhanced demonstration of individual components of the skull (Figure 7.2-4). Also the regions of interest have high inherent radiographic contrast, and CT provides clear, unobstructed images of the teeth. Disadvantages are the need for general anesthesia, specialized equipment, tables adapted for equine use, and proper positioning.

### Nuclear Scintigraphy

Because many dental disorders are associated with pathologic changes in adjacent bone, scintigraphic images may provide useful information regarding the exact tooth or teeth involved at an earlier stage than can be achieved with radiography. The advantages of nuclear scintigraphy over CT are that it can be performed in conscious animals and the equipment tends to be less expensive and more widely available. The disadvantages are potential radiation hazards; therefore strict control of radioisotope and patient handling are required. In a recent study with  $^{99m}\text{Tc}$ -methylene diphosphonate ( $^{99m}\text{Tc}$ -MDP), the sensitivity of scintigraphy for dental disease was excellent and the specificity was moderate, whereas the opposite results were obtained with radiography. The sensitivity and specificity were enhanced when both techniques were combined. Scintigraphy can aid the clinician in diagnosis by demonstrating an increased scintigraphic activity in the affected tooth compared with the contralateral tooth,



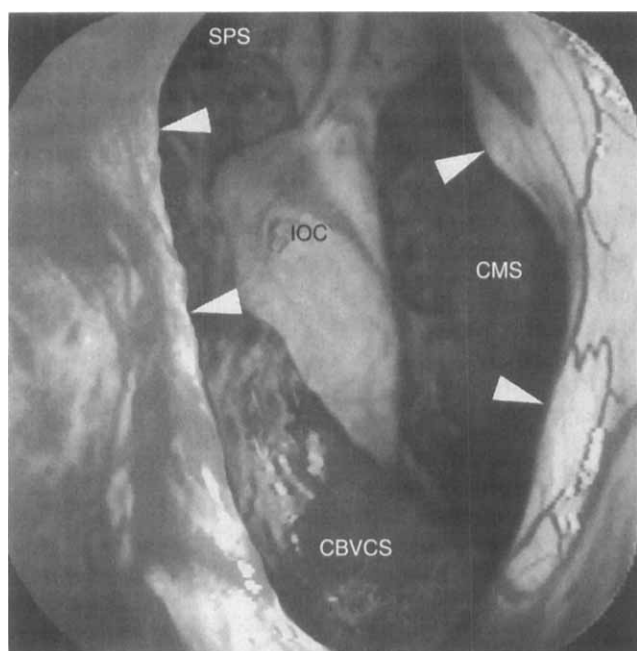
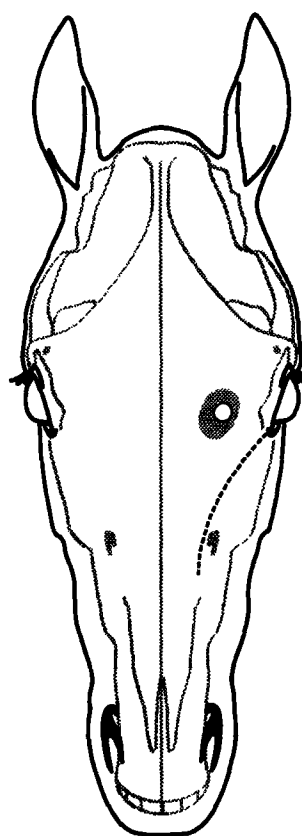
**Figure 7.2-4** Transverse view through head obtained by computed tomography at the approximate level of the fourth cheek tooth. DM, Dorsal meatus; FS, frontal sinus; DCS, dorsal conchal sinus; MM, middle meatus; VCS, ventral conchal sinus; NS, nasal septum; VM, ventral meatus; IOC, infraorbital canal and nerve; RMS, rostral maxillary sinus. Within the rectangle is a trauma-induced mild reaction in the nasal bones that would not be evident on routine radiographs.

with a typical pattern for different diseases. The anatomic detail obtained by scintigraphy allows precise localization of the disease process, although this detail diminishes with age, possibly because of decreased uptake of radio-pharmaceutical after the cheek teeth cease to erupt.

### Centesis

This procedure is used to sample fluid or to flush the sinuses and can be performed with the horse standing and mildly sedated. The site for centesis is determined by clinical and radiographic findings, but, if a generalized sinus problem is suspected, the preferred site is 2.5 to 3 cm dorsal to the facial crest and the same distance rostral to the medial canthus. If only the rostral maxillary sinus is involved, the area chosen for centesis is 3 cm dorsal to the facial crest and approximately 3 cm caudal to the infraorbital foramen. The site is clipped of hair, prepared for aseptic surgery, and infiltrated with local anesthetic. A 1-cm long incision is then made through the skin and subcutaneous tissues and a 2- to 4-mm diameter Steinmann pin attached to a Jacob's chuck is used to drill a hole through the bone. In some horses, a 16-gauge needle alone can be used to penetrate the bone without drilling a hole beforehand. Fluid within the sinus is aspirated and submitted for culture, Gram's stain, cytologic examination, and sensitivity testing. If the fluid is inaccessible or too viscous to aspirate, a small quantity of sterile saline that is free of bacteriostatic agents is injected into the sinus cavity to mix with fluid contents. The mixture is then aspirated. A large volume of fluid is then delivered by gravity into the sinus cavity. If the nasomaxillary opening is patent, fluid and exudate should flow freely from the nasal passage. Complications of centesis are rare, but purulent

**Figure 7.2-5** Site for inserting the endoscope for direct endoscopic examination of the sinuses, with the trephine site (circle) directly over the frontomaxillary opening (shaded).



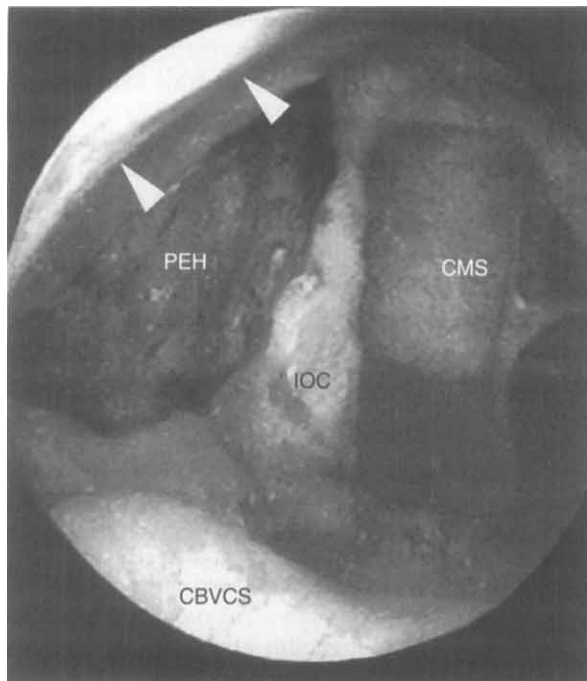
**Figure 7.2-6** View obtained through the flexible endoscope inserted into the left frontal sinus through the portal shown in Figure 7.2-5. Arrowheads indicate the edges of the frontomaxillary opening through which the following structures can be seen: caudal bulla of the ventral conchal sinus (CBVCS); infraorbital canal (IOC); caudal maxillary sinus (CMS); and sphenopalatine sinus (SPS). The caudal bulla of the ventral conchal sinus can vary in size and shape and should not be mistaken for a lesion. In this case, blood that has dripped from the portal can be seen on its surface.

material within the sinus can escape through the bone hole and induce local cellulitis.

### Direct Endoscopic Examination

Direct endoscopic examination is useful to diagnose diseases that are not readily detected on radiographs or nasal endoscopy. Sedation and local anesthesia can be used to insert an arthroscope or flexible endoscope into the sinuses to examine them directly or with a camera and monitor (Figure 7.2-5). The following portals are used: for the frontal sinus, 60% of the distance from midline towards the medial canthus and 0.5 cm caudal to the medial canthus (see Figure 7.2-5); for the caudal maxillary sinus, 2 cm rostral and 2 cm ventral to the medial canthus; and for the rostral maxillary sinus, 50% of the distance from the rostral end of the facial crest to the level of the medial canthus and 1 cm ventral to a line joining the infraorbital foramen and the medial canthus. One portal can be used for the endoscope and another to take a biopsy specimen. Direct endoscopic examination is more useful for examining the tooth roots of the second and third upper molars in horses older than 5 years than it is for rostral teeth in younger horses. Although this procedure is invasive, it is extremely informative and more sensitive than radiographs. However, if surgery is an option, the portal should not be made in the area of the proposed bone flap or the portal should be allowed to heal before surgery because it can predispose to fracture or necrosis of the bone flap.

The flexible endoscope is superior to the arthroscope used in the original descriptions of sinuscopy because it is more widely available and is more easily guided around the sinuses; thus it allows a more extensive examination (Figure 7.2-6). This endoscope does require larger portals,

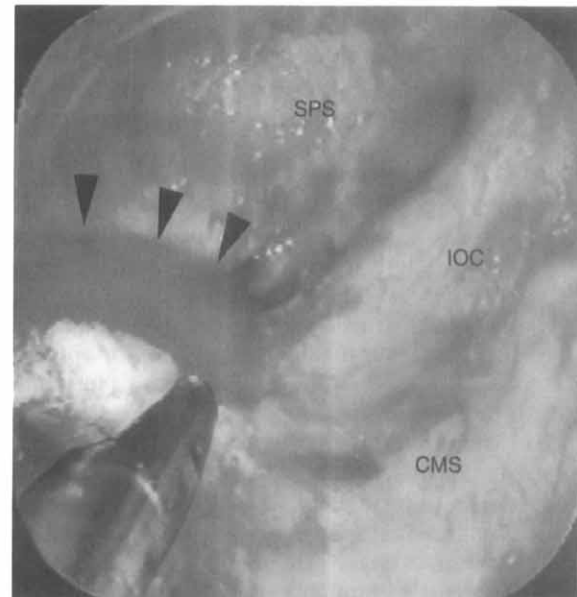


**Figure 7.2-7** Similar view obtained through the flexible endoscope as shown in Figure 7.2-6, but in a horse with a progressive ethmoid hematoma in the sphenopalatine sinus. This lesion could not be seen on nasal endoscopy nor on radiographs. *PEH*, Progressive ethmoid hematoma. (See Figure 7.2-6 for explanations of arrowheads and labels.)

however. The endoscope is sterilized by immersion in glutaraldehyde beforehand and then rinsed in sterile water or saline. To make the portal, a 2.5-cm long vertical skin incision is made, the underlying periosteum is reflected, and a hole is made in the bone with a 14-mm Michele trephine. The skin can be closed, or if the sinus is infected it can be left open to accommodate a lavage tube or allowed to heal by second intention. Rare complications are temporary periosteal reaction, cellulitis, and subcutaneous emphysema. Lesions diagnosed in this way include ethmoid hematomas (especially in unusual sites such as the sphenopalatine sinus; Figure 7.2-7), orbital floor fracture, neoplasia, sinusitis, and fungal infections. This approach can also be used for treatments that can be accomplished without a need for bone flaps. Biopsy specimens can be taken through a second portal under endoscopic guidance, or the same portal can be enlarged with rongeurs to allow insertion of a Ferris-Smith or intervertebral rongeur alongside the endoscope (Figure 7.2-8). These instruments can also be used to break down the caudal bulla of the ventral conchal sinus to create a portal for insertion of the endoscope from the frontal sinus portal into the rostral maxillary sinus or ventral conchal sinus (see Figure 7.2-6).

## DIAGNOSIS OF SINUSITIS

Primary sinusitis is caused by an upper respiratory tract infection that involves the paranasal sinuses, whereas secondary sinusitis is caused by a tooth root infection. Primary sinusitis usually involves all sinus cavities and causes dif-



**Figure 7.2-8** Similar view obtained through the flexible endoscope as shown in Figure 7.2-6 but in a horse with sinusitis. The endoscope has been inserted more fully through the frontomaxillary opening. Labels are the same as in Figure 7.2-6, but the arrowheads point to a fluid pocket in the sinuses. In the lower left corner, a Ferris-Smith rongeur can be seen inserted alongside the endoscope and through the same portal to grasp a piece of bone floating in the purulent contents.

fuse fluid opacification on radiographs. It can also be confined to the ventral conchal sinus, where it forms an abscess that is difficult to detect on radiographs. In secondary sinusitis, the teeth involved, in decreasing order of frequency, are the first molar, fourth premolar, and third premolar. Clinical signs of secondary sinusitis closely resemble those of primary sinusitis, including unilateral mucopurulent nasal discharge, and facial distortion in the more chronic stages. However, the nasal discharge may be fetid and sinus tracts can extend from the involved cheek teeth to the overlying skin. Radiographic findings are described in the text that follows.

## DIAGNOSIS OF DENTAL DISEASE

Interpretation of dental lesions requires an understanding of normal radiographic anatomy of the tooth root. In young horses, the root apices are smooth and round, but in older horses they become narrower and more pointed and eventually spicular. Also, the reserve crowns of cheek teeth become progressively shorter with advancing years. The roots of 109 and 209 (fourth cheek teeth) are ventral to the other roots, which reflects the early age of eruption, and the roots of 111 and 211 (sixth cheek teeth) tend to be set at an angle to the hard palate. The analogs of permanent teeth are evident in radiographs until the horse is approximately 4 years of age, when the sixth cheek tooth erupts. Eruption of a tooth is accompanied by an increase

in vascularity of the tooth pulp; this can be seen on radiographs as a cystic distention of the lamina dura. This change can be distinguished from an abscess by its smooth regular outline and association with an erupting tooth. The lamina dura is a radiographic white line that represents the alveolar bone and periodontal ligament interface, and the latter appears as a radiolucent line around the tooth root.

Signs of dental infections on lateral films are proliferative changes of osteitis of the maxilla adjacent to the infected tooth roots, such as localized, ill-defined areas of increased radiopacity and coarseness of the overlying bone texture. The radiographic signs of periapical disease are variable, but the most consistent sign is an area of increased lucency around the affected apex or apices, referred to as a *halo*. Loss of the lamina dura is a less reliable indicator of pathologic change, because this structure is an inconsistent feature on radiographs of normal horses. In many cases, the roots may be partly destroyed or distorted, increased in density, and clubbed. Fragments of unstructured mineralized tissue, sometimes adjacent to infected roots, are displaced fragments of the crown or deposits of cement. A granular pattern around a root can be caused by food material and gas bubbles, and fluid lines and gas-fluid interfaces can indicate anaerobic abscesses.

### DIAGNOSIS OF ETHMOID HEMATOMA

Ethmoid hematoma is a progressive and locally destructive mass of unknown cause in the paranasal sinuses that resembles a tumor in appearance and development but is not neoplastic. An expanding hematoma can cause pressure necrosis of surrounding bone but rarely causes facial distortion. It causes mild, persistent, and spontaneous intermittent and unilateral epistaxis in horses older than 6 years. The hematoma usually extends into the nasal passage and can be seen on endoscopy in the ethmoid turbinate region. On radiographs, large hematomas usually are seen on the ethmoid labyrinth, but smaller ones can arise from the floor of the sinuses. A hematoma confined to the sphenopalatine sinus (see Figure 7.2-7) cannot be seen on radiographs or on endoscopy of the nasal passages.

### DIAGNOSIS OF SINUS CYSTS

Sinus cysts are single or loculated fluid-filled cavities with an epithelial lining that develop in the maxillary sinuses

and ventral concha and can extend into the frontal sinus. A congenital form has been described, but most sinus cysts can be found in horses over a wide age range. The major clinical signs are facial swelling, nasal discharge, dullness on percussion, and partial airway obstruction. Radiographs are more helpful than endoscopic examination for diagnosis, and they can demonstrate multiloculated densities and fluid opacities in the sinuses, occasionally with dental distortion and displacement, flattening of tooth roots, soft tissue mineralization, and considerable deviation of the nasal septum and vomer bones.

### DIAGNOSIS OF MISCELLANEOUS DISEASES

Malignant tumors of osseous, connective, and epithelial tissues tend to occur in older horses and are usually manifested by signs similar to those of sinusitis and even ethmoid hematoma. Radiographic signs are aggressive bone destruction in the presence of normal teeth that may or may not be displaced. Fungal granulomas caused by *Coccidioides* organisms or *Cryptococcus* organisms can cause similar clinical and radiographic findings as neoplasia. The diagnosis of a skull fracture is based on a history of trauma, clinical signs such as epistaxis, evidence of an open or closed wound, subcutaneous emphysema, and palpation of a bony deficit or depressed bone. Detached skin can maintain normal facial contour. Although radiographs are necessary for assessment of sinus fractures, they provide inadequate information about the extent of the fracture, because they can only image it in a two-dimensional mode.

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## CHAPTER 7.3

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# Progressive Ethmoid Hematoma

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A progressive ethmoid hematoma (PEH) is a slowly expanding, nonneoplastic mass that usually originates from the submucosa of the nasal or sinus portion of the ethmoid labyrinth. PEH is idiopathic and occurs only in horses. Hemorrhage from a congenital or acquired hemangiomas lesion into the submucosa of the ethmoid labyrinth has been proposed to be the pathogenic mechanism by which PEH occurs.

The PEH mass destroys adjacent tissue while recurrent hemorrhage causes the mass to slowly expand along the lines of least resistance into the nasopharynx, ipsilateral and contralateral nasal passages, or the adjacent paranasal sinuses. In rare cases a PEH may originate from the submucosa of areas of the paranasal sinuses other than the ethmoid labyrinth; masses that do arise from regions other than the ethmoid labyrinth are more likely to remain small. The condition usually occurs unilaterally, but approximately 15% of affected horses are affected bilaterally.

### SIGNALMENT

The prevalence of PEH is low; at referral hospitals the disease is reportedly seen in approximately one horse per 2500 (0.04%). Horses with PEH represent 8% of horses with diseases of nasal cavity and paranasal sinuses. Horses affected with PEH may be any age, but middle-aged and old horses are more likely to be affected. The average age of affected horses is approximately 10 years. Horses younger than 3 years are seldom affected, but PEH has been reported in a 4-week-old foal. The disease has been reported to occur in most breeds, a notable exception being the Standardbred, but the disease seems to have a predilection for the Arabian and Thoroughbred breeds. The prevalence of the disease does not differ between males and females or between geldings and stallions, but females are significantly more likely than males to develop bilateral PEH.

### CLINICAL SIGNS

The most common clinical sign of PEH is scanty, intermittent, usually nonodorous, and hemorrhagic or sero-hemorrhagic discharge from the affected, and sometimes the unaffected, nasal passage. Hemorrhage is caused by ulceration of the lesion's capsule, and although hemorrhage is usually spontaneous, it is sometimes precipitated by exercise. Another common sign of PEH is reduced airflow through one or both nasal cavities. Airflow can be reduced

directly by a lesion within the nasal cavity or indirectly by a lesion within the paranasal sinuses that causes distortion of the medial wall of the sinuses into the ipsilateral nasal cavity. A large lesion can deviate the nasal septum into the contralateral nasal cavity. Obstruction of the nasal cavity can result in stertorous respiration at exercise or at rest and even in respiratory distress.

Other signs may include episodes of coughing, head shaking, halitosis, exophthalmos, facial deformity, purulent nasal discharge, and choking and excessive salivation. The lesion may be visible at an external naris. The condition may occasionally be accompanied by submandibular lymphadenopathy. Results of complete blood count and serum biochemical evaluations of affected horses are usually normal but may reveal anemia. The interval of time between the occurrence of a PEH and initiation of clinical signs is not known, and it is likely that small lesions may cause no clinical signs of disease.

Other conditions that may resemble PEH because they cause epistaxis include facial trauma; septic pneumonia; mycosis of the guttural pouch; infection of a nasolacrimal duct; exercise-induced pulmonary hemorrhage; rupture of the longus capitis and rectus capitis ventralis muscles; and neoplasia of the lungs, larynx, pharynx, nasal cavities, paranasal sinuses, or guttural pouches. Lesions of the nasal passages that endoscopically resemble PEH include polyps, fungal masses, and neoplasia.

### DIAGNOSIS

A PEH may appear radiographically, on lateral and dorso-ventral projections, as an abnormal, nonmineralized opacity of soft-tissue density with a smooth margin ventral to the eye and rostral to the ethmoid labyrinth. The lesion is usually best seen on a lateral projection. Small lesions, especially those within the ethmoid recess, may be obscured by superimposition of the eyes and ethmoid labyrinth. Fluid lines within the paranasal sinuses may be noted if the lesion lies with the paranasal sinuses. Positive contrast sinusography or computed tomographic imaging may allow the extent of a lesion to be more completely evaluated. Computed tomography allows the structures of the head to be viewed without superimposition.

Endoscopic evaluation of the nasal cavity of the affected side may reveal a yellow, red, and green mass that appears to originate from the nasal portion of the ethmoid labyrinth. The color of the mass depends on the type and



distribution of the hemoglobin pigments present after the most recent hemorrhage within the lesion. Fungal plaques may be present on the lesion. A large mass may obscure its origin, and the mass may protrude caudally around the nasal septum into the contralateral nasal cavity, which obscures the contralateral ethmoid labyrinth and gives the impression that the horse has two masses instead of one. Both nasal cavities should always be examined endoscopically because the condition occurs bilaterally in approximately 15% of affected horses.

If a PEH originates from the sinus portion of the ethmoid labyrinth, the mass is not seen during endoscopic examination of the nasal cavity unless it erodes into the nasal cavity or protrudes into the nasal cavity through the nasomaxillary aperture or the dorsal or ventral ethmoid meati. Hemorrhage may be seen emanating from the ventral or dorsal ethmoid meati or at the caudal end of the middle nasal meatus where it escapes from the paranasal sinuses through the nasomaxillary aperture. A lesion within the paranasal sinuses can usually be observed through an arthroscope or flexible endoscope inserted into the caudal maxillary or conchofrontal sinus through a trephine hole.

Diagnosis of PEH is often based on clinical signs displayed by the affected horse and endoscopic appearance of the lesion, but histologic examination of the lesion confirms the diagnosis. An endoscopic biopsy instrument is usually ineffective in obtaining sufficient tissue required for histologic diagnosis, but adequate tissue required for histologic diagnosis can be obtained with a uterine biopsy instrument directed to the lesion by using endoscopic guidance.

The lesion is composed of a thick, fibrous capsule covered with respiratory epithelium, (which may be ulcerated in places) that overlies a fibrous stroma filled with old and recent hemorrhage in various stages of phagocytosis. The hemorrhage gives the cut surface of the mass a reddish-brown color. Within the hemorrhage are hemosiderin-filled macrophages, multinucleated giant cells in densely packed foci, and inflammatory infiltrate composed of plasma cells, lymphocytes, and (less commonly) neutrophils and eosinophils. Mineralization of collagen fibers and areas of necrosis are often histologic features.

## TREATMENT

Treatment of affected horses is destruction of the PEH, including its origin. Affected horses have been treated by surgical excision of the mass; pernasal cryogenic ablation; surgical excision combined with cryogenic ablation; pernasal, transendoscopic, laser photoablation; surgical excision combined with laser photoablation; and transendoscopic injection of a solution of formaldehyde into the lesion. Removal of a PEH from two horses by means of a snare placed around the pedicle of the lesion with endoscopic guidance has been reported, and spontaneous resolution of PEH has been observed.

## Surgical Ablation

Surgical ablation is usually performed through an osteoplastic, frontonasal flap, but an osteoplastic maxillary flap

may be required in some cases. The osteoplastic flap is created with the horse anesthetized and positioned in lateral recumbency. A PEH arising from the sinus portion of the ethmoid labyrinth is exposed for excision through the osteoplastic flap. To remove a PEH that has arisen from the nasal portion of the ethmoid labyrinth, the floor of the dorsal conchal sinus, exposed by the frontonasal flap, must be fenestrated to expose the middle nasal meatus and the mass contained within. The PEH is excised, and the portion of the ethmoid labyrinth from which the lesion has arisen is destroyed with a large curette or abraded with a gauze sponge.

A common, serious complication of surgical ablation of a PEH is severe intraoperative hemorrhage. Creation of the frontonasal flap generally causes only mild hemorrhage, but perforation of the dorsal conchal sinus into the nasal cavity and excision of the PEH are usually accompanied by severe hemorrhage. To avoid cardiovascular complications associated with severe hemorrhage, the horse should receive intravenously administered isotonic fluids during anesthesia. Although replacement of blood is seldom necessary, having at least 4 L of blood available for transfusion may be advisable, especially if the surgeon is inexperienced in the procedure. If the horse is anemic before surgery, blood from an appropriate donor should be administered during or before surgery.

Techniques used to control hemorrhage during surgery include temporarily packing the nasal cavity and paranasal sinuses with gauze (either dry or saturated with epinephrine) and temporarily occluding both carotid arteries. To temporarily occlude the carotid arteries during surgery, snares are placed around each common carotid artery in the anesthetized horse before sinusotomy. While the lesion is being removed, the clinician tightens the snares to occlude the arteries. The carotid arteries can be occluded for at least 15 minutes without causing neurologic deficits. The advantage of controlling hemorrhage by occluding the carotid arteries must be weighed against the disadvantages of prolonging the anesthesia and the risk of injury to the recurrent laryngeal nerves or the vagosympathetic trunks. These nerves lie adjacent to the arteries and can be damaged during placement and removal of the snares. Because of the presence of the circle of Willis, occlusion of the common carotid arteries does not always prevent severe hemorrhage.

Removal of a PEH with the horse standing and its head elevated may decrease the severity of hemorrhage by lowering the horse's blood pressure. The advantages of performing the surgery with the horse standing include convenience and elimination of anesthetic risk, but these advantages must be weighed against the problems that could be encountered during surgery if the horse hemorrhages severely while its head cannot be properly restrained.

If the PEH has been removed from the nasal portion of the ethmoid labyrinth through a fenestration in the dorsal conchal sinus, it is usually necessary to pack both the affected nasal cavity and the paranasal sinuses to control hemorrhage. The nasal cavity and the paranasal sinuses can be packed individually with separate rolls of gauze, or the sinuses and nasal cavity can be packed with one continuous roll of gauze. The end of the gauze that exits the nasal cavity should be sutured to the nostril to prevent

complete loss of the gauze should the horse accidentally swallow the pack. If the nasal cavity is packed separately, an elastic, tubular stocking can be inserted into the nasal cavity and then filled with gauze packing; this method prevents the horse from swallowing the gauze. If the PEH has been removed from the sinus portion of the ethmoid labyrinth, only the paranasal sinuses need be packed. The end of the gauze roll exits through a small trephine opening created adjacent to the osteoplastic flap. The pack can usually be removed safely from the sinuses or the nasal cavity at 24 to 48 hours. If severe hemorrhage occurs after the pack is removed from the nasal cavity, the packing must be reintroduced. Lavage of the paranasal sinuses with isotonic saline solution after the pack is removed is not imperative, but it removes blood clots, which helps to decrease the amount and duration of nasal discharge.

Other complications associated with surgical ablation have included suture periostitis, dehiscence of the cutaneous wound; death from meningoencephalitis or intracranial hemorrhage; sequestration of a portion of the osteoplastic flap; and opportunistic fungal infection at the surgery site.

### Cryogenic Ablation

Ablation of PEH by application of a cryogen, such as liquid nitrogen delivered as a spray or through a probe, or Freon delivered as a spray, causes minimal hemorrhage. With endoscopic guidance the clinician can administer the cryogen through the nose with the horse conscious and standing. This type of cryoablation is used only to treat horses with small lesions on the nasal portion of the ethmoid labyrinth. A cryogen, preferably liquid nitrogen, can also be applied through a large cryosurgical probe or as a spray to the base of the lesion after the lesion has been surgically ablated.

To destroy the origin of a PEH with a cryogen, hemorrhage must be controlled temporarily after the lesion has been surgically ablated. Hemorrhage control is necessary because uncontrolled hemorrhage prevents effective application of the cryogen. The clinician can press gauze sponges firmly over the origin of the lesion and then progressively expose small areas of the lesion for application of the cryogen; this procedure controls hemorrhage that occurs after the lesion has been excised. Another method of hemorrhage control is to freeze the intact PEH and then remove frozen sections piecemeal until the entire lesion has been removed and its origin frozen. If the cribriform plate is inadvertently frozen, severe complications from damage to the brain may result. Thermocouples can be used to ensure that the temperature at the level of the cribriform plate does not fall below  $-10^{\circ}\text{C}$ .

Application of a cryogen to the base of the lesion after the lesion has been surgically ablated has been reported to result in a lower incidence of recurrence. However, another report that examined the effects of application of a cryogen to the base of the PEH during surgery found no such advantage.

### Ablation by Laser

Progressive ethmoid hematomas less than 5 cm in diameter located on the nasal portion of the ethmoid laby-

rinth can be ablated through an endoscope by use of a neodymium/yttrium-aluminum-garnet (Nd:YAG) laser. The horse must be sedated and standing and a topical anesthetic must be applied to the nasal passage. Lesions are best photoablated by use of a noncontact technique at 60 W. The interval between treatments should be at least 7 days to allow devitalized tissue to slough. Photoablation of a small PEH usually requires multiple treatments, and the cost of equipment may limit the practicality and availability of the technique.

To excise a PEH with laser assistance, the lesion is exposed through an osteoplastic, frontonasal flap, and the attachment of the origin of the lesion is severed with the laser. Laser-assisted excision may allow transection of the PEH closer to its origin than is possible with surgical ablation alone. Transendoscopic ablation of PEH with an Nd:YAG laser has been reported to result in less hemorrhage and fewer recurrences, but one study found that laser-assisted excision of PEH seemed to offer no distinct advantage over traditional techniques in prevention of the lesion.

### Chemical Ablation of Progressive Ethmoid Hematoma

A PEH can be ablated through an endoscope with use of a 4% aqueous solution of formaldehyde gas (created by diluting a 37%-40% aqueous solution of formaldehyde gas with 9 parts of water [i.e., 10% formalin]). This method avoids complications such as excessive hemorrhage. With the horse standing and sedated, formaldehyde solution is delivered through stiff polypropylene tubing, the end of which has been beveled to penetrate the capsule of the lesion. The tubing is inserted through the biopsy channel of the endoscope. Instead of beveling the tubing, the clinician can fit the tubing with a hypodermic needle without a hub. The needle is retracted into the biopsy channel of the endoscope while the insertion tube of the endoscope is inserted into the nasal cavity. Once the endoscope is correctly placed, the catheter and needle are advanced into the lesion. The lesion can also be injected with the use of commercially available polypropylene tubing to which has been swaged a 23-gauge needle (Mill-Rose Laboratories, Mentor, Ohio). The clinician injects small lesions by inserting only the needle into the center of the mass. To inject the center of large lesions, the needle is advanced until it and the end of the tubing have been inserted into the center of the lesion.

Depending on their size, lesions are injected with 1 to 100 ml of formaldehyde solution until the lesion distends and begins to leak solution. The horse is treated periodically until the lesion is eliminated or is so small and deep within the ethmoid labyrinth that injecting the lesion is no longer possible. Treatment of horses whose lesion does not protrude beyond the external lamina of the ethmoid bone may not be necessary because lesions of this size often cause no clinical signs of disease. If the horse is treated at 3- to 4-week intervals, usually only 2 to 5 treatments are required regardless of the size of the lesion.

A lesion on the sinus portion of the ethmoid labyrinth can also be injected by means of an endoscope inserted through a trephine hole into the caudal maxillary or conchofrontal sinus. Injection of only the nasal portion of a

lesion that extends from the nasal portion of the ethmoid labyrinth into the adjacent paranasal sinuses may cause both the sinus and nasal portions of the lesion to resolve.

One horse with a PEH treated by chemical ablation developed laminitis within 24 hours after each of three treatments. Signs of laminitis resolved on each occasion after administration of a nonsteroidal antiinflammatory drug. The link between injection of formaldehyde solution and development of laminitis may have been coincidental, nevertheless systemic administration of a nonsteroidal antiinflammatory drug before injection of formaldehyde solution may be warranted to help avoid this complication.

### PROGNOSIS

Distortion of a nasal cavity that is caused by deviation of the paranasal sinuses from the mass contained within resolves within weeks after the mass has been removed, and a deviated nasal septum may return to its normal position. Distorted facial appearance caused by a PEH is also likely to eventually resolve after the lesion is removed.

Regardless of the method by which a PEH is ablated, the prognosis for long-term cure is guarded to poor. The incidence of recurrence after surgical excision is reported to range from approximately 14% to approximately 45%. Bilaterally affected horses are far more likely to experience recurrence of the lesion than are unilaterally affected horses. Incomplete excision may, in part, account for the high incidence of recurrence of PEH, or a new PEH may develop in adjacent or distant sites.

Determination of which treatment is most effective in preventing recurrence is difficult because comparing the effects of various methods of treating affected horses is difficult. In published studies of horses affected with PEH, horses were examined for recurrence at different times after surgery; in many studies, horses displaying no clinical signs of disease were not examined endoscopically. After treatment both nasal cavities of affected horses should be endoscopically examined at least twice yearly for at least 5 years to determine whether the lesion has reappeared, but the length of time after which a lesion is unlikely to recur has not been determined.

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## CHAPTER 7.4

# Axial Deviation of the Aryepiglottic Folds

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**A**xial deviation of the aryepiglottic folds (ADAF) has been recognized as a cause of dynamic upper respiratory obstruction in horses since the first use of high-speed treadmill exercise testing to evaluate poor performance. The membranous portions of the aryepiglottic folds, which extend from the abaxial margin of the epiglottis to the corniculate processes at the lateral aspect of the arytenoid cartilages, collapse axially to occlude the glottis during inspiration (Figure 7.4-1). Horses with ADAF have poor performance and are often reported to "finish poorly" or "stop" near the end of a race. During inspiration at exercise, some affected horses make an abnormal

noise that may sound similar to the "roar" associated with laryngeal hemiplegia. The cause is unknown, although immaturity may be a factor in younger horses and should be suspected if concurrent dynamic upper respiratory abnormalities are present.

### CLINICAL SIGNS AND DIAGNOSIS

Affected horses are typically presented with a chief complaint from the owner of poor performance. Horses with ADAF may or may not make an abnormal upper respiratory noise during exercise. No breed or gender predisposi-

lesion that extends from the nasal portion of the ethmoid labyrinth into the adjacent paranasal sinuses may cause both the sinus and nasal portions of the lesion to resolve.

One horse with a PEH treated by chemical ablation developed laminitis within 24 hours after each of three treatments. Signs of laminitis resolved on each occasion after administration of a nonsteroidal antiinflammatory drug. The link between injection of formaldehyde solution and development of laminitis may have been coincidental, nevertheless systemic administration of a nonsteroidal antiinflammatory drug before injection of formaldehyde solution may be warranted to help avoid this complication.

### PROGNOSIS

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Regardless of the method by which a PEH is ablated, the prognosis for long-term cure is guarded to poor. The incidence of recurrence after surgical excision is reported to range from approximately 14% to approximately 45%. Bilaterally affected horses are far more likely to experience recurrence of the lesion than are unilaterally affected horses. Incomplete excision may, in part, account for the high incidence of recurrence of PEH, or a new PEH may develop in adjacent or distant sites.

Determination of which treatment is most effective in preventing recurrence is difficult because comparing the effects of various methods of treating affected horses is difficult. In published studies of horses affected with PEH, horses were examined for recurrence at different times after surgery; in many studies, horses displaying no clinical signs of disease were not examined endoscopically. After treatment both nasal cavities of affected horses should be endoscopically examined at least twice yearly for at least 5 years to determine whether the lesion has reappeared, but the length of time after which a lesion is unlikely to recur has not been determined.

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## CHAPTER 7.4

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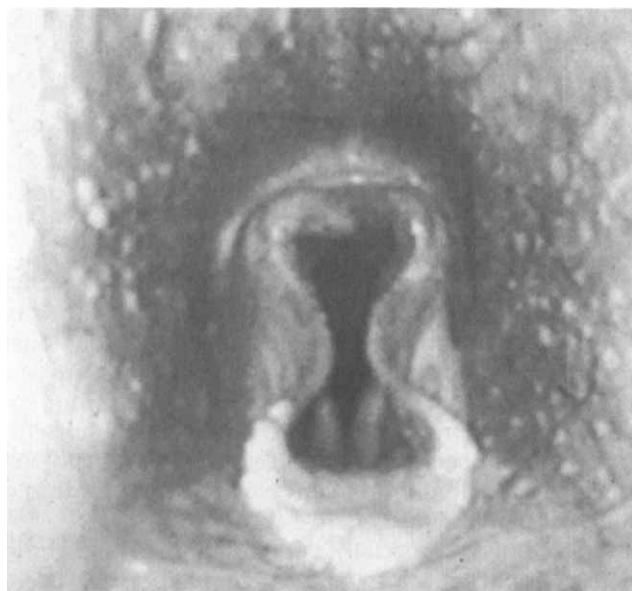
DANA STAUNTON KING  
*Madison, Wisconsin*

**A**xial deviation of the aryepiglottic folds (ADAF) has been recognized as a cause of dynamic upper respiratory obstruction in horses since the first use of high-speed treadmill exercise testing to evaluate poor performance. The membranous portions of the aryepiglottic folds, which extend from the abaxial margin of the epiglottis to the corniculate processes at the lateral aspect of the arytenoid cartilages, collapse axially to occlude the glottis during inspiration (Figure 7.4-1). Horses with ADAF have poor performance and are often reported to "finish poorly" or "stop" near the end of a race. During inspiration at exercise, some affected horses make an abnormal

noise that may sound similar to the "roar" associated with laryngeal hemiplegia. The cause is unknown, although immaturity may be a factor in younger horses and should be suspected if concurrent dynamic upper respiratory abnormalities are present.

### CLINICAL SIGNS AND DIAGNOSIS

Affected horses are typically presented with a chief complaint from the owner of poor performance. Horses with ADAF may or may not make an abnormal upper respiratory noise during exercise. No breed or gender predisposi-



**Figure 7.4-1** Still image from an endoscopic examination performed on an exercising horse. Bilateral axial deviation of the aryepiglottic folds is shown.

tion exists, and the condition has been diagnosed in Thoroughbreds, Standardbreds, and racing Arabians. The condition has been reported in racehorses from 2 to 8 years of age, but the percentage of 2- and 3-year-old horses that were diagnosed with ADAF in one hospital population was significantly greater than in the overall hospital population evaluated for poor performance.

Physical examination and endoscopic examination of the resting horse typically do not yield any abnormalities related to the condition. At endoscopic examination at rest, the membranous portion of the aryepiglottic folds of affected horses has no visible structural or functional abnormalities. Nasal occlusion during endoscopic examination, which mimics airway pressures generated during exercise, does not induce ADAF in horses that subsequently demonstrate the condition during treadmill exercise. Endoscopic examination during high-speed treadmill exercise is required to diagnose ADAF. ADAF most often occurs as a distinct clinical problem but also can occur with other upper airway abnormalities. Horses may be unilaterally or bilaterally affected. No association has been identified between the development of ADAF and subsequent dorsal displacement of the soft palate or other causes of dynamic upper respiratory abnormalities.

Severity of ADAF is evaluated based on the extent to which the membranous portion of the aryepiglottic folds collapse across adjacent structures of the larynx. With mild collapse, the fold remains abaxial to the vocal fold. Moderate cases have collapse of the fold beyond the vocal fold but less than halfway between the vocal fold and the midline. In severe collapse, the fold reaches or crosses the midline of the glottis. Mild collapse results in less than or equal to 20% obstruction of the glottis and may not be of clinical significance in some cases. Horses with moderate collapse have 21% to 40% obstruction of the glottis and

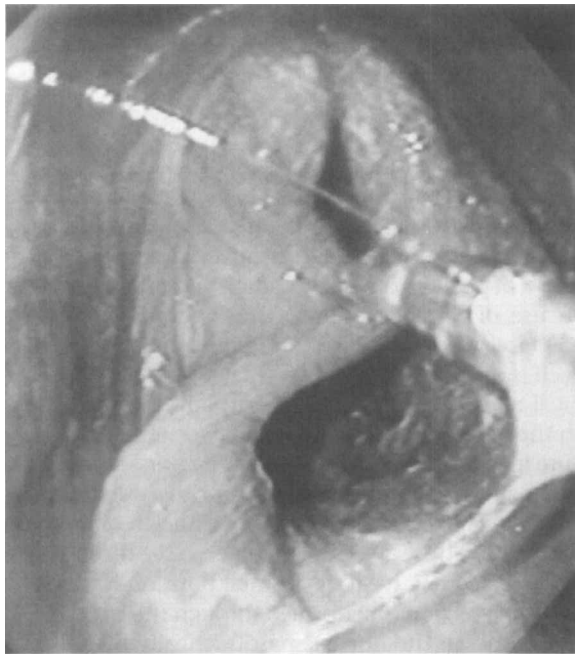
those with severe collapse have been reported to have 41% to 63% obstruction.

## TREATMENT

Horses with moderate and severe cases of ADAF and those with clinically significant mild ADAF are candidates for surgical treatment. Transendoscopic laser excision of the aryepiglottic folds (TLEAF) to remove a 2-cm isosceles right triangle of tissue from each collapsing aryepiglottic folds with use of a neodymium/yttrium-aluminum-garnet or diode laser in contact fashion is recommended. This approach is easier to perform in a sedated, standing horse with topical anesthesia, but it may be performed successfully with the horse anesthetized in lateral recumbency. The procedure may also be performed with the horse under general anesthesia through a laryngotomy with conventional instruments. The disadvantage for the clinician of performing the procedure this way is the inability to see the exact tissue being resected relative to its normal position to the larynx. If surgical resection is performed through the laser with general anesthesia, the horse is nasotracheally intubated and heliox (70% helium, 30% oxygen) should be mixed with 100% oxygen to achieve a fraction of oxygen in inspired air equal to 0.4 to prevent ignition while the laser is activated.

For surgery with TLEAF in the standing animal, horses are sedated with xylazine hydrochloride (0.4 mg/kg IV). Additional doses of xylazine hydrochloride (0.2 mg/kg IV) may be required. A videoendoscope is inserted into the nasal passage ipsilateral to the target aryepiglottic fold and held in place by an assistant. Topical anesthesia is achieved with an aerosolized solution that contains benzocaine hydrochloride (14%), butyl aminobenzoate (2%), and tetracaine hydrochloride (2%; Cetacaine) administered through polyethylene tubing (PE-240; Becton Dickinson, Sparks, Md.) passed through the biopsy channel of the videoendoscope.

Bronchoesophagoscopy forceps (Richard Wolf Medical Instrument, Vernon Hills, Ill.), 60 cm in length and bent manually to conform to the curve of the equine nasal passage and pharynx, are used to provide traction on the aryepiglottic folds during excision. These forceps are passed into the nasal passage contralateral to the target aryepiglottic fold and are manipulated by a second assistant. The free margin of the membranous portion of the aryepiglottic fold is grasped halfway between the arytenoid and epiglottic attachments and elevated caudodorsally (Figure 7.4-2). The laser is set to 18 W of power and excision of the tissue is performed in contact fashion. Beginning rostrally and immediately adjacent to the epiglottic attachment, the clinician makes a horizontal incision in the mucosa by sweeping the fiber side to side and gradually cutting tissue in a rostral to caudal direction. The grasping forceps are then rotated to apply traction to the aryepiglottic fold in a rostromedial direction. A vertical incision is then made from dorsal to ventral to cut the tissue adjacent to its attachments on the corniculate process of the arytenoid cartilage. The vertical incision is extended ventrally to intersect the horizontal incision and the tissue is removed with the grasping forceps. For bilateral excision, the videoendoscope and forceps are positioned in reverse for excision of the contralateral aryepiglottic fold.



**Figure 7.4-2** Before the resection is begun, the right aryepiglottic fold is grasped with the bronchoesophageal forceps and checked for proper positioning through reproduction of the deviation observed during exercise.

To excise the aryepiglottic fold with the horse under general anesthesia, the horse's mouth is held open with a mouth speculum and the soft palate is manually displaced dorsally. Active suction is used to evacuate smoke from the pharynx. The videoendoscope, grasping forceps, and suction tubing are all positioned in the oral cavity to perform the same surgical procedure. Surgical excision has been performed through a laryngotomy; however, this approach does not afford the same visual perspective of the surgical field as does the videoendoscopic approach.

Broad-spectrum antimicrobial therapy is given preoperatively and continued for 7 days postoperatively because of the open mucosal wound created in the larynx by excision of the aryepiglottic fold. Antiinflammatory therapy is recommended and should consist of tapering courses of phenylbutazone (2 mg/kg orally twice daily for 3-4 days, then once daily for 3-4 days), prednisolone (0.8 mg/kg orally once daily for 7 days, then 0.8 mg orally every other day for 3 treatments then 0.4 mg/kg orally every other day for 3 treatments), in addition to a topical pharyngeal spray (37 ml nitrofurazone solution [0.2%], 12 ml dimethyl sulf-

oxide [DMSO; 90%], 50 ml glycerine, and 0.2 ml prednisolone acetate [5%]; 10 ml twice daily for 7 days). The pharyngeal spray is administered through a 10-Fr male dog urinary catheter (Monoject, division of Sherwood Medical, St Louis, Mo.) that is placed up the ventral meatus of the nasal passage to a point level with the medial canthus of the eye. The pharyngeal spray is given slowly. If the horse swallows during administration, the catheter is correctly placed in the pharynx.

Postoperative management instructions for horses that have TLEAF should include at least two weeks of daily hand-walking or turnout in a small paddock. Additional rest may be indicated if other surgical procedures are performed for concurrent airway problems. Follow-up endoscopy is recommended before returning the horse to training. Postoperatively, the edge of the tissue will look slightly more fibrous and concave but not dramatically different than the preoperative appearance.

Some horses, especially younger animals and those with multiple upper respiratory abnormalities, may benefit from conservative management with prolonged rest. Additionally, these horses may benefit from longer periods of time between races when returned to training.

## PROGNOSIS

In a retrospective study of racehorses with an exclusive diagnosis of ADAF as the cause of their poor performance, 75% of horses that had surgical excision of the aryepiglottic folds and 50% of the horses managed with rest had improved performance. Improvement of the upper respiratory noise is more likely to occur with surgical treatment. No complications have been recognized after surgical excision, and no adverse effects on deglutition or laryngeal or pharyngeal function have been reported.

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## CHAPTER 7.5

## Arytenoid Chondrosis

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**A**rytenoid chondrosis is a disease of one or both arytenoid laryngeal cartilages that results in varying degrees of respiratory compromise. The disorder results from ascending inflammation and/or infection into the body of the arytenoid cartilage through a mucosal disruption on the axial side of the cartilage at the level of the glottis. The inflammation results in distortion and swelling of the cartilage, obstructs the laryngeal lumen, and compromises both inspiration and expiration. Most commonly observed in Thoroughbred racehorses, arytenoid chondrosis is seen in all breeds of all ages.

## DIAGNOSIS

Diagnosis of arytenoid chondrosis should be made on the basis of historic clinical information, palpation of the larynx, and the resting endoscopic examination. The disorder may be seen in an acute, subacute, or chronic stage. The acute stage involves dramatic laryngeal and perilaryngeal inflammation and edema; infrequently an associated cellulitis will be present in the throat latch region. Horses will often be presented as an emergency for severe respiratory distress and stridor. Typically, previously observed mucosal abnormalities in these horses will not have caused any clinical abnormalities until the acute stage. The severity of the mucosal swelling during the acute phase prohibits accurate assessment of the final conformational changes to the cartilage. Not until aggressive medical treatment is administered can the final shape and function of the arytenoid be determined.

The diagnosis of arytenoid chondrosis is easy to make in the acute cases but not in the more subtle or chronic cases. With increasing expectations for performance and the increasing number of times a horse is examined endoscopically, clinicians see a greater number of horses with early signs of chondrosis without profound perilaryngeal inflammation. In the chronic stage, no laryngeal edema is present but abnormalities to the shape of the corniculate process can be seen. During endoscopic examination of a resting horse, cartilaginous protrusions are often observed on the axial side of the arytenoid near the vocal process. Furthermore, coexisting superficial "kissing" lesions often exist on the apposing arytenoid that may appear more significant than those seen on the surface of the affected arytenoid. In rare instances no lesions are seen at the opening of the larynx but ulcerative lesions are present just inside the laryngeal lumen that are difficult to observe because of the horse swallowing during the examination. The degree of respiratory stridor is commensurate with the degree of arytenoid deformity and obstruction.

Some degree of concurrent compromised abduction of the affected arytenoid is usually present. It is assumed that a degree of laryngeal hemiplegia precedes the chondrosis, which accounts for some of the limitations of abduction. Concurrent swelling of the arytenoid cartilage will also be present, which results in a mechanical restriction of the movement of the arytenoid. Before treatment options are considered, it is important to differentiate a grade IV hemiplegia from an arytenoid cartilage that is structurally abnormal as a result of chondritis. Normally no space will exist between an immobile grade IV hemiplegic arytenoid and the palatopharyngeal arch, which makes the rim of the arch difficult to see endoscopically. If a space lateral to the corniculate cartilage exists and the palatopharyngeal arch can be clearly seen, this indicates structural enlargement of the arytenoid (Figure 7.5-1). This abnormality can also be palpated externally. Although a horse with a grade IV laryngeal hemiplegia has a very prominent muscular process, the chondritic arytenoid does not and will be less defined.

Differentiation of arytenoid chondrosis from an uncomplicated laryngeal hemiplegia should be based on endoscopic appearance, arytenoid movement, and external palpation of the larynx. The clinician must determine



**Figure 7.5-1** Chondropathy of the left arytenoid. Note the abnormal shape of the corniculate cartilage, the cartilaginous projection on left arytenoid, the visibility of the palatopharyngeal arch behind the left arytenoid, and the kissing granulation tissue on the right arytenoid cartilage.



whether arytenoid chondrosis exists before deciding on the treatment, because chondrosis and hemiplegia must be managed differently.

## TREATMENT

### Medical Treatment

Acute inflammation associated with an arytenoid chondrosis can be treated aggressively with intravenous (IV) antimicrobials and antiinflammatory drugs, and may not require surgical intervention. Because it is difficult to get a bacterial culture to direct treatment, broad-spectrum antimicrobials are used. Potassium penicillin (22,000 IU/kg q6h), gentamicin (6.6 mg/kg q24h), phenylbutazone (4.4 mg/kg q12h), and dexamethasone (0.025-0.05 mg/kg q24h) are given intravenously. Because respiratory distress can be induced with any excitement, the horse should be kept in a quiet environment and monitored closely. An emergency tracheotomy kit should be kept stallside. Tracheotomy is reserved for situations in which the animal cannot be maintained in a quiet environment or when respiratory stridor is evident even when the animal is relaxed.

Within a few days dramatic improvement usually occurs with a decrease in the soft tissue swelling. Surgery is still not recommended at this point because many horses will continue to improve for 30 days with further rest and antimicrobial treatment. Horses are discharged with recommendations for oral antimicrobial treatment and 30 days of rest before endoscopic reevaluation to assess the need for further treatment. Horses that do not show dramatic improvement within the first few days on IV antimicrobial treatment, have gross purulent material draining from their arytenoid, or have swelling of the laryngeal saccule are taken to surgery more quickly. Swelling of the saccule indicates accumulation of purulent material abaxial to the arytenoid.

Further treatment is often predicated on the response to medical treatment and the proposed use of the horse. Several horses have gone back to racing after medical treatment alone despite having slightly abnormal looking corniculate processes of their arytenoids. These horses maintain good arytenoid abduction bilaterally. Those horses that have granulation tissue remaining on their arytenoid are best treated by laser excision of the tissue and rest. Several weeks are required for the mucosa to cover the defect before exercise can be resumed. If laryngeal function is still compromised sufficiently to compromise the horse's athletic purpose, a partial arytenoidectomy should be considered. If the horse is intended to return to athletic performance, the clinician should ensure that one arytenoid has full function. If not it is unlikely an arytenoidectomy will be enough to return the horse to full athletic function.

### Surgical Treatment

A temporary tracheotomy must be performed so that the horse can be given anesthetic gas during the surgical procedure of partial arytenoidectomy. If too much laryngeal compromise exists initially, the tracheotomy should be performed with the horse standing to guarantee the horse

a patent airway during induction of anesthesia. If a large enough lumen is present that an endotracheal tube can be passed through the larynx after anesthesia is induced, the tracheotomy is performed with the horse under general anesthesia and the endotracheal tube switched to the tracheotomy site once the horse has been anesthetized. This method will allow for a cleaner, smaller tracheotomy. Caution should be exercised so the tracheotomy site is not placed too far cranially. The position of the tracheotomy relative to that of the larynx is deceptive when the horse is under anesthesia and the head extended. If the tracheotomy is placed too far cranially it may become obstructed during recovery from anesthesia.

To perform an arytenoidectomy a standard laryngotomy approach is first made to the larynx. A headlamp is very useful for illumination while the clinician is working within the larynx. Placement of the endoscope through the nares in front of the larynx can also supplement light. Multiple techniques exist for performing partial arytenoidectomy. It is always best to try and salvage a mucosal flap on the axial side of the arytenoid to achieve primary mucosal closure after the arytenoid is removed to minimize the prospect of granulation tissue formation postoperatively. Before performing the arytenoidectomy, the clinician should remove the vocal chord and ventricle. This procedure leaves an opening at the ventral aspect of the arytenoidectomy site for any drainage of submucosal hemorrhage or clot abaxial to the final mucosal flap.

To form the mucosal flap, mucosal incisions are made from dorsal to ventral at the caudal border of the arytenoid and the rostral border, just caudal to the corniculate. These incisions are connected in a horizontal incision along the ventral border of the arytenoid. The mucosa is slowly dissected free from the arytenoid and left attached dorsally. The abaxial border of the arytenoid is then freed of its muscular attachments with primarily blunt dissection to minimize hemorrhage. The muscular process is isolated and transected. The clinician then elevates the arytenoid and frees it completely by cutting the remaining corniculate mucosa rostrally. Any remaining dorsal attachments are also cut and the cricoarytenoid joint capsule is cut caudally. Mucosa is held together to plan closure, and excess mucosa is trimmed. The caudal edge of the mucosal flap is apposed to the laryngeal mucosa in a simple continuous pattern with absorbable suture, with the clinician working dorsal to ventral. The rostral edge of the mucosal flap is apposed similarly to the remaining mucosa that was abaxial to the corniculate, in a parallel line to the caudal edge. The most difficult part of the incision is its very dorsal aspect; it is extremely important to close the dorsal aspect to prevent the formation of granulation tissue. The ventral aspect is left open to drain. Bleeding should be minimal once the mucosal edges are apposed. Any granulating "kissing" lesions on the opposite arytenoid should be debrided at this time. If extensive purulent material exists abaxial to the arytenoid, a mucosal closure is not performed. At the conclusion of surgery the endotracheal tube can be replaced with an equivalent size tracheotomy tube for the horse's recovery from general anesthesia.

On the morning after surgery another endoscopic examination should be performed. A clear opening to the



glottis should exist; if the clinician holds off the tracheotomy tube while watching the horse's respiratory effort, laryngeal function can be assessed. If laryngeal function is adequate for the horse to breathe easily through its nares, the tracheotomy tube can be removed. The horse should be maintained on perioperative antimicrobials and antiinflammatories for 1 week while being maintained in a stall for 1 month. During this time, the horse can be allowed to graze under hand restraint. The tracheotomy and laryngotomy sites are left open to heal in by second intention. All feeding should take place from the ground to minimize the risk of aspiration. An endoscopic examination should be performed 1 month postoperatively to determine the presence of granulation tissue. Once mucosal healing is complete the horse should receive a 1-month turnout before resuming exercise.

Several potential complications of this surgery exist. The most common complications after an arytenoidectomy are granulation tissue or excessive residual mucosa. The clinician should remove this substance at the first month by videoendoscopic laser excision performed with the horse standing under sedation. If it is not removed in the early stages, the tissue may mineralize and make excision much more difficult later. A more serious, life-threatening complication is aspiration pneumonia. The risk of pneumonia may be dramatically decreased by less traumatic dissection of the arytenoid from the lateral musculature at the time of surgery. Many of these muscle bellies narrow the glottis while the horse swallows, thus playing a protective role. Another complication is postoperative noise. This postoperative respiratory noise most likely originates from vibration of the residual arytenoid/corniculate mucosa. An examination performed with the horse on a treadmill may be beneficial to make this deter-

mination. The adjacent aryepiglottic fold that is no longer held abaxially by the arytenoid can be the offending soft tissue that obstructs the airway. This tissue, or any residual arytenoid mucosa, can be identified during an endoscopic examination performed while the horse is exercising on a high-speed treadmill. The tissue should be removed as needed.

## PROGNOSIS

The prognosis for horses with arytenoid chondrosis is extremely variable and depends on the extent of the disease and the time to treatment. Many horses with a mild form of chondrosis in a chronic, nonactive state can function quite adequately. Horses with concurrent severe hemiplegia or more severe chondrosis will likely require surgical intervention to provide an airway for any athletic function. Most of these horses will return to athletic function but will have a decrease in their racing or athletic ability. Horses with severe bilateral disease are very unlikely to return to any significant athletic function.

## Supplemental Readings

- Tulleners EP, Harrison IW, Raker CW: Management of arytenoid chondropathy and failed laryngoplasty in horses: 75 cases (1979-1985). *J Am Vet Med Assoc* 1988; 192(5):670-675.
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## CHAPTER 7.6

# Laryngeal Hemiplegia in Non-Racehorses

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**A**bnormal inspiratory noise is a common upper respiratory problem in both racehorses and non-racehorses, and laryngeal hemiplegia is the most common cause of abnormal inspiratory noise in the exercising horse. Laryngeal hemiplegia is a result of recurrent laryngeal neuropathy that leads to atrophy of the intrinsic laryngeal muscles, particularly the cricoarytenoideus dorsalis. Progressive atrophy of the cricoarytenoideus dorsalis

prevents proper abduction of the arytenoid cartilage, thus the cross-sectional area of the laryngeal opening is decreased. This decrease in the size of the airway causes increased inspiratory resistance, decreased inspiratory flow, abnormal inspiratory noise, and varying degrees of exercise intolerance.

The etiology of recurrent laryngeal neuropathy is usually idiopathic, however, *Streptococcus equi* abscessation,

glottis should exist; if the clinician holds off the tracheotomy tube while watching the horse's respiratory effort, laryngeal function can be assessed. If laryngeal function is adequate for the horse to breathe easily through its nares, the tracheotomy tube can be removed. The horse should be maintained on perioperative antimicrobials and antiinflammatories for 1 week while being maintained in a stall for 1 month. During this time, the horse can be allowed to graze under hand restraint. The tracheotomy and laryngotomy sites are left open to heal in by second intention. All feeding should take place from the ground to minimize the risk of aspiration. An endoscopic examination should be performed 1 month postoperatively to determine the presence of granulation tissue. Once mucosal healing is complete the horse should receive a 1-month turnout before resuming exercise.

Several potential complications of this surgery exist. The most common complications after an arytenoidectomy are granulation tissue or excessive residual mucosa. The clinician should remove this substance at the first month by videoendoscopic laser excision performed with the horse standing under sedation. If it is not removed in the early stages, the tissue may mineralize and make excision much more difficult later. A more serious, life-threatening complication is aspiration pneumonia. The risk of pneumonia may be dramatically decreased by less traumatic dissection of the arytenoid from the lateral musculature at the time of surgery. Many of these muscle bellies narrow the glottis while the horse swallows, thus playing a protective role. Another complication is postoperative noise. This postoperative respiratory noise most likely originates from vibration of the residual arytenoid/corniculate mucosa. An examination performed with the horse on a treadmill may be beneficial to make this deter-

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prevents proper abduction of the arytenoid cartilage, thus the cross-sectional area of the laryngeal opening is decreased. This decrease in the size of the airway causes increased inspiratory resistance, decreased inspiratory flow, abnormal inspiratory noise, and varying degrees of exercise intolerance.

The etiology of recurrent laryngeal neuropathy is usually idiopathic, however, *Streptococcus equi* abscessation,

guttural pouch infection, or trauma to the recurrent laryngeal nerve from perivascular injection of irritating substances. Most commonly the left arytenoid cartilage is affected, however, paralysis of the right arytenoid does occur and in rare cases the condition is bilateral and causes severe airway obstruction. Significant documentation exists of the effects of laryngeal hemiplegia in the racehorse; however, little has been published about the disease in performance horses. Because of the different demands placed on non-racehorses, treatment as well as prognosis can be quite varied.

## DIAGNOSIS

Diagnosis is based on clinical signs as well as physical examination and dynamic endoscopic examination findings. Physical examination should include palpation of the laryngeal area for prominence of the muscular process of the arytenoid cartilage. The muscular process will palpate as a distinct “knuckle” cranial to the dorsal border of the thyroid cartilage on the affected side. Varying degrees of atrophy of the overlying muscle, the cricoarytenoideus dorsalis, will determine how prominently the muscular process palpates. Palpation will also help determine if the horse has evidence of a previous surgery or if the horse has thickening and loss of normal architecture suggestive of arytenoid chondritis. A thorough physical examination should include assessment of both jugular veins for thrombosis, thrombophlebitis, or perivascular thickening. These findings are more commonly associated with right-sided hemiplegia.

Endoscopic or videoendoscopic examination can be performed in both the resting and exercising horse. Routine examination of the upper respiratory tract includes evaluation of the larynx, nasal cavity, nasopharynx, cervical trachea, and guttural pouch openings. Endoscopic evaluation of the airway of the nonsedated, resting horse should reveal a rhythmic increase in abduction of the arytenoid cartilages during inspiration. Various techniques, such as nasal occlusion and induced swallowing, can be employed to induce movement of the larynx to allow dynamic evaluation. The appearance of the airway immediately after swallowing has been induced by instilling water through the endoscope, is more representative of the airway during exercise, and is better tolerated by the horse than manual occlusion of the nasal passages. The time of maximal abduction achieved after swallowing is very short, however, and laryngeal movements must be assessed quickly. A comparison is made between the movements of the left and right arytenoids. The degree of synchrony and amount of abduction is graded on a scale of I to IV. Horses that have synchronous, complete abduction and adduction of the laryngeal cartilages are designated grade I. In contrast, grade IV horses have marked asymmetry of the arytenoids with no movement of one of the arytenoids during any phase of respiration. Grade II hemiplegia is characterized by asynchronous movements of the arytenoids, however, the horse is able to achieve full abduction after nasal occlusion or swallowing. Grade III horses will have asynchronous movement of the arytenoids at rest and full abduction is not inducible. Grades II and I are considered to be normal.

Further dynamic evaluation of arytenoid function is performed in the exercising horse during treadmill endoscopy. This method is a useful way to assess whether horses with grade III hemiplegia are able to attain and maintain normal abduction during exercise. During treadmill examination, grade III horses can be further categorized into IIIA, IIIB, and IIIC. Grade IIIA horses can maintain almost full abduction throughout the exercise period, grade IIIB attain and maintain only partial abduction, and grade IIIC horses are unable to maintain any significant abduction of the arytenoid cartilage during exercise.

## CLINICAL SIGNS AND RISK FACTORS FOR LARYNGEAL HEMIPLEGIA

Regardless of the horse's occupation, the primary presenting complaint that leads to a suspicion of laryngeal hemiplegia is abnormal noise during exercise with or without varying degrees of exercise intolerance. However, the signalment can be different. The average age of presentation of the performance horse is 7.7 years, 4 years older than the average age of the presenting racehorse. In addition, size, breed, and gender appear to be physical characteristics that affect the incidence of laryngeal hemiplegia. The incidence of laryngeal hemiplegia in Thoroughbred horses has been reported to range from 2.6% to 8.3%. Laryngeal hemiplegia occurs significantly more frequently in large horses, with as many as 50% of horses more than 17 hands tall being affected. Conversely, the disease is rare in horses less than 15 hands and almost never occurs in ponies. Because size affects the incidence of laryngeal hemiplegia, it would follow that large breeds would be at an increased risk for the disease. In one study that included 29 different breeds presented and diagnosed with laryngeal hemiplegia, breed risk factors included Percheron, Belgian, Clydesdale, Thoroughbred, and American Saddlebred breeds. Several investigations have shown that geldings and stallions are at increased risk of developing laryngeal hemiplegia relative to mares. The reason for the size, age, breed, and gender variations is unknown.

## CLINICAL SIGNIFICANCE

Racehorses with laryngeal hemiplegia often are presented for poor performance rather than just for the accompanying abnormal inspiratory noise. The reduction in inspiratory airflow that occurs with laryngeal hemiplegia is exacerbated during maximal exertion. Not only is the arytenoid cartilage unable to fully abduct, but it dynamically collapses into the airway with the increase in negative pressure that develops during inspiration and with the fatigue of the cricoarytenoideus dorsalis muscle. Event and steeplechase horses can also experience poor performance associated with laryngeal hemiplegia because they compete at high exertional levels over significant distances.

Exercise intolerance is not only a problem in performance horses at high exertional level. Intolerance can occasionally be a complaint in English pleasure and dressage horses and similar horses that work at lower exertional levels. Head and neck flexion characteristic of such animals during exertion exacerbates their clinical signs. Approximately 75% of inspiratory resistance occurs in the

upper airway in the exercising horse. Any condition that decreases the cross-sectional area in the upper airway further increases inspiratory resistance. Head and neck flexion alone can cause upper airway obstruction by decreasing the cross-sectional area of the respiratory tract; this obstruction can result in an almost twofold increase in inspiratory impedance. For these horses it is not only important to definitively determine the etiology of the exercise intolerance, but also to clearly define the career goals for the horse. If the horse is allowed to work with less head and neck flexion, at a lower level, or in a different class, the exercise intolerance can sometimes be resolved without surgical intervention. It is also important to remember that even with resolution of exercise intolerance, inspiratory noise may continue to be present. Typically an abnormal noise is an earlier clinical sign of hemiplegia that occurs before an effect on exercise tolerance is observed. Noise can occur before there is significant airway obstruction.

Show horses may present for inspiratory noise without any exercise intolerance. Inspiratory noise may be career-limiting or just an incidental finding depending on the expectations for the horse. An example within the American Horse Show Association (USA Equestrian) is dressage horses versus American Saddlebred horses. As stated in the American Horse Show Association (USA Equestrian) Rule Book, any horse with "broken wind" may compete in dressage competitions. In contrast, any evidence of "broken wind" with or without clinical signs will disqualify an American Saddlebred or hackney horse. Therefore depending on the competition, laryngeal hemiplegia that causes upper respiratory noise may or may not be tolerated. All breed and competition standards must be evaluated independently when the future of the horse is being considered.

## EVALUATION OF LARYNGEAL FUNCTION

Various treatment options are available for laryngeal hemiplegia. However, besides changing the form of competition, all recommended treatments are surgical. Surgical treatment options include ventriculocordectomy, laryngoplasty ("tieback") or a combination of both techniques, and finally arytenoidectomy. Horses with grade IV idiopathic laryngeal hemiplegia are adversely affected or penalized for almost all types of competition and should benefit from surgical intervention. One true exception is the jumper. Noise does not affect performance scores, and often a horse can breathe well enough between jumps to compete effectively. Some less severely affected grade III horses require more than an endoscopic examination at rest to make a clear determination of the significance of the hemiplegia. This determination is most reliably made during an endoscopic examination performed while the horse is exercising on a treadmill. This examination should be performed with the horse in tack and simulating the approximate head carriage during competitions if possible. Horses with grades IIIB and IIIC paresis are clinically affected and should benefit from surgical treatment. If treadmill facilities are unavailable an attempt should be made to rule out other causes of respiratory noise and exercise intolerance based on the characteristics of the noise made

during exercise. Differential diagnoses include epiglottic entrapment, epiglottic retroversion, pharyngeal collapse, axial deviation of the aryepiglottic folds, and dorsal displacement of the soft palate.

If a horse demonstrates mild grade III hemiplegia on an endoscopic examination made at rest but does not have significant dynamic collapse during exercise, frequent endoscopic reevaluations should be performed. Although grade III hemiplegia has not been shown to progress to grade IV in every case, such progression does often occur. Some reports exist of improved laryngeal function over time but there is little physiologic evidence to explain this improvement. If no other reasonable explanation can be found for the upper respiratory noise and the horse cannot attain full abduction after swallowing, the horse is likely to experience dynamic collapse of that side during exercise and surgery should be considered an appropriate treatment. Treatment modality and prognosis are further influenced by the career goals for the horse. Successful outcome for any therapy is determined by the definition of success. Success in a racehorse may be elimination of exercise intolerance with or without elimination of the upper respiratory noise. For hunters, American Saddlebred horses, or draft horses that show in harness, success consists not only of eliminating exercise intolerance but also more importantly of eliminating abnormal respiratory noise.

## TREATMENT

One component of the abnormal noise associated with hemiplegia emanates from the vibration of the slack vocal cord. An older procedure to try and stabilize the cord was the ventriculectomy. A variation of that older procedure is the ventriculocordectomy. Ventriculocordectomy is aimed at completely eliminating the vocal cord from collapsing into the airway by removing it rather than just trying to stabilize it. It has been shown that ventriculectomy alone does not improve airflow in experimental conditions, however, in clinical studies the procedure has been reported to somewhat improve upper respiratory noise and occasionally exercise intolerance associated with laryngeal hemiplegia. More recently the importance of removing the entire vocal cord to decrease respiratory noise and provide a larger airway has been established. One advantage to performing either a unilateral or bilateral ventriculocordectomy is that the procedure can often be done in the standing horse. In very mild cases of hemiplegia, this procedure alone may be sufficient to resolve the problem of respiratory noise.

Laryngoplasty is still the treatment of choice for most cases of laryngeal hemiplegia. This procedure has been shown experimentally to improve airflow and has been shown to return airflow to prehemiplegia levels in horses exercised at speeds less than a fast gallop (15-17 m/sec). It has also been shown to be effective clinically with success rates for racehorses of 50% to 70% and as high as 86% for performance horses. Laryngoplasty and ventriculocordectomy are often performed during the same surgery. Ventriculocordectomy with laryngoplasty returns the cross-sectional area of the rima glottidis to normal but laryngoplasty alone does not. Postoperative noise occurs

less frequently with ventriculocordectomy and laryngoplasty than laryngoplasty alone. On the basis of endoscopic examinations made while horses exercised on a treadmill and on anecdotal information, ventriculocordectomy with laryngoplasty is thought to benefit horses more than laryngoplasty alone.

Finally, arytenoidectomy is an option typically reserved for horses that have had ineffective laryngoplasty procedures. Partial arytenoidectomy (removal of all of the arytenoid cartilage except for the muscular process) is the method of choice over subtotal arytenoidectomy (preserves the muscular and corniculate processes) when arytenoidectomy is indicated. This procedure inherently results in a smaller airway than a successful laryngoplasty and has greater potential for continued abnormal respiratory noise during exercise since the structural support of the mucosa is removed. Despite these mitigating factors, arytenoidectomy can also be successful.

In summary, laryngeal hemiplegia is a common cause of exercise intolerance and upper respiratory noise in the non-racehorse population. This condition is most successfully managed surgically by laryngoplasty in conjunction with ventriculocordectomy procedures. The treat-

ment of exercise intolerance may be more rewarding than the treatment of upper respiratory noise. Upper respiratory noise is a problem specific to many disciplines of the performance horse and it is sometimes the most challenging to resolve.

### Supplemental Readings

- Hawkins JE, Tulleners EP, Ross MW et al: Laryngoplasty with or without ventriculectomy for treatment of left laryngeal hemiplegia in 230 racehorses. *Vet Surg* 1997; 26:484-491.
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## CHAPTER 7.7

# Guttural Pouch Disease

CLAUDE A. RAGLE  
*Pullman, Washington*

The guttural pouches are paired diverticula of the eustachian tubes that connect the middle ear to the pharynx for the purpose of pressure equalization. The guttural pouches, which serve the function of selective brain cooling, are positioned between the base of the skull, the ventral straight muscles of the head and the atlas dorsally, and the pharynx and beginning of the esophagus ventrally. The pouch is folded over the rostral aspect of the stylohyoid bone where it creates a medial and lateral recess. The dorsal wall of the medial recess contains the glossopharyngeal nerve (cranial nerve IX) and the vagus (cranial nerve X), as well as the pharyngeal branches of these nerves. The accessory nerve (cranial nerve XI), the hypoglossal nerve (cranial nerve XII), the sympathetic trunk with the cranial cervical ganglion, and the internal carotid artery are also in the wall of the medial recess. The lateral recess contains the maxillary vessels and the external carotid artery.

### GUTTURAL POUCH EMPYEMA

Horses with empyema (pus in a body cavity) of the guttural pouch(es) are most often presented because of puru-

lent nasal discharge. The guttural pouches open into the nasopharynx caudal to the point at which the nasal passages are completely divided by the nasal septum. This structure causes the discharge to be bilateral even if only one pouch is affected. Another common clinical sign is increased respiratory noise. Some horses may show signs of retropharyngeal swelling, coughing, and/or dysphagia. Fever may or may not be present. The most consistently measured change in blood analysis is a slight increase in fibrinogen concentration.

Diagnosis of guttural pouch empyema is based on consistent clinical signs, a thorough examination, and a complete history. The goals of diagnostics include confirmation of the site of origin of the nasal discharge and/or the cause of the increased respiratory noise. In addition the clinician must determine whether one or both pouches are affected, because 60% of horses have bilateral disease. Each pouch should be examined for the presence of exudate. Samples should be collected for culture and cytology and the exudate should be evaluated to determine its consistency. If the exudate becomes inspissated, solid clumps of pus called *chondroids* can form. The clinician should also confirm that the nasopharyngeal openings

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Diagnosis of guttural pouch empyema is based on consistent clinical signs, a thorough examination, and a complete history. The goals of diagnostics include confirmation of the site of origin of the nasal discharge and/or the cause of the increased respiratory noise. In addition the clinician must determine whether one or both pouches are affected, because 60% of horses have bilateral disease. Each pouch should be examined for the presence of exudate. Samples should be collected for culture and cytology and the exudate should be evaluated to determine its consistency. If the exudate becomes inspissated, solid clumps of pus called *chondroids* can form. The clinician should also confirm that the nasopharyngeal openings

into the guttural pouches are patent and free of adhesions or deformity.

Endoscopy is extremely useful in the diagnosis of guttural pouch infection. If the horse is demonstrating clinical signs at the time of the examination the clinician can easily determine whether exudate is present in the pouches. The clinician can pass the endoscope into the guttural pouch by passing an endoscopic biopsy forceps through the biopsy channel of the endoscope and into the pharyngeal opening of the guttural pouch. This procedure is performed on the same side as the endoscope is passed. The entire endoscope is rotated (slowly, so as to not torque fibers or cables) without advancing. Because the biopsy channel is offset from center of the endoscope, rotation of the endoscope displaces the cartilage flap that forms the medial aspect of the pharyngeal orifice of the guttural pouch. By not advancing the endoscope during rotation, the clinician can clearly view displacement of the flap and simultaneously direct and advance the endoscope through the vestibule and into the guttural pouch. Once the endoscope is inside the pouch, samples can be obtained and a thorough evaluation of both medial and lateral recesses can be performed. Endoscopic access to the guttural pouch may be impossible because of fibrosis of the vestibule as a result of severe inflammation. Manipulation of the flap and vestibule with a Chambers mare catheter passed through the opposite nasal passage during endoscopic viewing can confirm obstruction. In addition to the guttural pouches, the nasopharyngeal area is evaluated to detect any encroachment of the dorsal or lateral pharyngeal walls as a result of guttural pouch distention. The soft palate is closely observed for signs of displacement or dysfunction during deglutition. If dysphagia has been noted, endoscopic examination of the trachea is warranted to assess potential feed contamination of the airway. The larynx should also be critically evaluated for symmetry and normal function.

Radiographic evaluation of the guttural pouches can be very informative and is fundamental when endoscopy is not possible. It is important to realize that radiography and endoscopy are complimentary and not mutually exclusive.

## Treatment

Treatment of guttural pouch empyema is based on several principles, the foremost being drainage and lavage. The role of systemic antibiotics in the treatment of guttural pouch empyema is uncertain, but general agreement exists that systemic antibiotic treatment alone is often unsuccessful. Less consensus exists as to whether a systemic antibiotic combined with lavage is superior to lavage alone or lavage spiked with antiseptics or antibiotics alone. Administration of systemic antibiotics in conjunction with guttural pouch lavage (with or without antiseptics or antibiotics) is recommended until a comparative clinical study indicates otherwise. Penicillin or ceftiofur are good choices pending results of culture and sensitivity. Trimethoprim-sulfamethoxazole is a poor choice as common isolates from guttural pouch empyema (e.g., *Streptococcus* spp.) are often resistant. Selection of the proper fluids for lavage of the guttural pouch is important. The solution should not induce a significant inflammatory re-

sponse. Topical mixtures that induce tissue damage and cellular death potentiate infection. Polyionic fluids are best. Saline (0.9%) can induce a slight inflammation, but this is considered clinically insignificant. Any addition of antibiotic or antiseptic to the fluids should preserve the tissue compatibility of the solution. A typical frequency and duration of lavage is once per day for 4 to 6 days. If lavage is required for more than a week, the frequency is usually reduced to every other day. The horse must be sedated for treatment so that the head is lowered to allow outward drainage toward the nostrils. This position will reduce the risk of aspiration during lavage. In severely affected horses a tracheostomy may be required before lavage to ensure unobstructed respiration and prevention of aspiration.

Lavage fluid is infused into the affected pouch with either a Chambers mare catheter or a uterine infusion pipette. Fluids (usually 500-1000 ml) are slowly instilled until overflow is observed, and then the pouch is allowed to drain. This process is repeated (usually 2-3 times) until clear effluent is achieved. Other tube devices can be used as long as they can be passed into the pouches. The largest diameter catheter that can be safely passed is helpful for unimpeded retrograde flow of lavage fluid and exudate. It is a good idea to view the pouch endoscopically after lavage to monitor the progress of exudate removal. It can also be helpful to provide additional sedation if required to assure that the horse's head will be lowered for another 15 to 20 minutes after lavage to provide for an enhanced drainage period. If culture results indicate the presence of *S. equi*, care should be taken with lavage and housing of affected horses to minimize environmental contamination. Attention to these details is an important part of the overall disease management for the farm or hospital.

Surgical treatment of guttural pouch empyema is indicated if inspissated pus and/or loss of patency of the nasopharyngeal orifice are present. Surgical treatment has also been recommended when empyema is unresponsive to medical therapy. When large amounts of inspissated pus become entrapped in the guttural pouches, surgical intervention is required for removal. If the chondroids are few in number and small in size, removal with endoscopic viewing and a basket snare may be possible. Successful treatments of chondroids with lavage (with or without acetylcysteine) have been reported. A solution of 20 to 60 ml of 20% acetylcysteine is infused, and the horse's head is kept elevated for 20 minutes to hold the fluid in the pouch. The infusion is repeated 4 times during a 30-day period. Alternatively, 300 ml normal saline without acetylcysteine can be instilled daily for 24 days through a 10-F indwelling catheter.

Chondroid removal is most commonly performed through either a modified Whitehouse or Viborg surgical approach. Surgical removal has the advantage of immediate results from a single treatment. Endoscopic viewing of all areas of the pouch should accompany the operation because the entire pouch cannot be viewed and easily accessed through the surgical incision. Endoscopic assistance can insure complete removal of all chondroids at surgery. Complete removal is extremely important for sustained resolution of the clinical signs. Without the endoscopic viewing at surgery, a significant risk exists of incomplete removal. Surgeons experienced

with the procedure should perform surgical operations of the guttural pouches to minimize possible complications.

Fistulation of the auditory tube diverticulum is recommended to establish drainage of the guttural pouch when loss of patency of the orifice exists. Fistulation is most commonly performed with laser or electrosurgery to create an opening just dorsal and caudal to the nasopharyngeal orifice. The same effect (i.e., nasopharyngeal fistula into the guttural pouch) can be achieved with aggressive resection of the cartilaginous flap through a Viborg or modified Whitehouse approach. After either surgical procedure, an indwelling Foley catheter is placed for approximately 14 days to prevent closure of the fistula during healing. The same surgical treatment has been reported as an adjunct to resolve chronic guttural pouch tympany that has been unresponsive to medical treatment alone. The creation of the nasopharyngeal fistula is hypothesized to allow improved drainage of the guttural pouch that leads to resolution of the disease.

### GUTTURAL POUCH TYMPANY

Guttural pouch tympany is a condition of young horses in which excessive air is trapped in the pouch(es). This condition is likely the result of dysfunction of the nasopharyngeal orifice of the guttural pouch that causes it to act as a one-way valve. The causes of this dysfunction are unknown. Foals are most commonly presented at 2 to 4 months of age (range, 4 days to 20 months) with a characteristic tympanitic swelling of the Viborg region. Additional signs are respiratory noise, cough, and dysphagia.

Diagnosis of guttural pouch tympany is based on consistent clinical signs, a thorough examination, and a complete history. Diagnostic procedures must determine whether the condition is unilateral or bilateral and assess whether concurrent disease processes such as guttural pouch empyema or aspiration pneumonia present. To make these determinations a complete blood count and measurement of plasma fibrinogen are necessary. Endoscopic examination is useful to determine the degree of nasopharyngeal compromise and presence of empyema. Samples should be collected for culture if exudate is detected. Selective catheterization or endoscopy and deflation of a pouch can clarify whether the condition is unilateral or bilateral. The soft palate is closely observed for signs of displacement or dysfunction during deglutition. If dysphagia or coughing has been noted, endoscopic examination of the trachea is warranted to assess potential feed contamination of the airways. The larynx is also evaluated for symmetry and normal function. Often it is best to reserve final conclusions about nasopharyngeal and laryngeal function until resolution of the tympany following surgical treatment. Horse owners must be informed that preexisting neuromuscular dysfunction may not improve in spite of treatment. Radiographic evaluation of the guttural pouches can provide important information regarding the presence of empyema and the degree of airway narrowing. If coughing and/or dysphagia with tracheal contamination are suspected, radiographic and ultrasound examination of the chest will assess pulmonary involvement. Ultrasound and endoscopy are complementary and not mutually exclusive.

### Treatment

The goal of treatment is to prevent excessive air trapping in the guttural pouches. Additionally, any accompanying respiratory infection and inflammation should be treated. If the condition is unilateral, fenestration of the medial septum is the accepted procedure. This method allows entrapped air from the affected side to exit through the opposite functional nasopharyngeal orifice. Fenestration can be created endoscopically by use of laser or electrosurgery. Alternatively, the stoma can be made with forceps and scissors through a Viborg or modified Whitehouse approach. The fenestration must be made as large (greater than 2-3 cm) as the nerves and vessels in the medial septum will allow. If the stoma is not large enough it may close during healing and tympany will recur. During surgery passage of an endoscope into the opposite pouch allows transillumination of the medial septum. This procedure helps to identify the best area of the septum, free of neurovascular structures, for resection.

If both pouches are tympanitic, fenestration is combined with resection of one nasopharyngeal orifice. A 2.5-cm × 1.5-cm portion of the cartilaginous medial flap is resected through a Viborg or modified Whitehouse approach. Another procedure resects the plica salpingopharyngea, which is attached to the cartilage of the medial lamina of the vestibule at the entry to the guttural pouch. Some confusion exists in the surgical texts as to the exact nomenclature and landmarks of tissues for resection. From a practical standpoint the ostium to the inside of the pouch has the appearance of two thin, apposing, dorsoventrally oriented lips. The medial lip contains the auditory tube cartilage and the lateral lip is formed by portions of the tensor and levator veli palatini muscles. This author prefers to resect the entire lateral lip only and leave the medial lip intact. In this author's experience this method prevents entrapment of air in the pouch and makes the development of adhesions within the vestibule less likely to occur. With this technique no indwelling catheter is required after surgery. This author also prefers to close the approach incision to create an immediate air-tight seal and thus confirm the function of the resected ostium. No negative effects on nasopharyngeal function from removal of these portions of the tensor and levator veli palatini muscles have been noted to date. An alternative technique is fistulation of the auditory tube diverticulum. This method is performed endoscopically in the sedated foal with laser or electrosurgery to create an opening just dorsal and caudal to the nasopharyngeal orifice. It is important with this technique that an indwelling Foley catheter is placed for approximately 14 days to prevent closure of the fistula during healing.

The prognosis for uncomplicated guttural pouch tympany is very good. It is important that owners be informed that tympany may recur in 10% to 30% of the foals. Prognosis worsens with the severity and duration of concurrent diseases.

### GUTTURAL POUCH MYCOSIS

Guttural pouch mycosis is the most common cause of serious epistaxis that is not related to exercise or trauma. Massive epistaxis may be the first and only outward clinical sign of fungal invasion of the guttural pouch. In other



horses, infection results in chronic mucoid or serosanguineous nasal discharge, with or without cranial nerve dysfunction. Depending on which nerves are affected, signs can include neuromuscular dysfunction of the pharynx (dysphagia, coughing, abnormal respiratory noise, or persistent displacement of the soft palate), Horner's syndrome, or laryngeal hemiplegia. Life-threatening hemorrhage occurs when the wall of a major artery is eroded.

Diagnosis of guttural pouch mycosis is based on consistent clinical signs, a thorough examination, and a complete history. Several important diagnostic goals should be noted. The source of the discharge or hemorrhage must be identified. Endoscopy allows viewing of the mycotic lesion in the guttural pouch and confirms the source of the bleeding. The most common site of hemorrhage is the internal carotid artery and, to a lesser extent, branches of the external carotid artery. Guttural pouch mycosis forms a brownish or greenish or white plaque on the wall of the pouch. This plaque is usually located on the dorsocaudal aspect of the medial recess. Samples can be collected for cytology and culture during endoscopy, but care should be taken not to disturb areas near the arteries. The most common isolates are *Aspergillus fumigatus* or *nidulans* (also known as *Emmericella nidulans*).

The second main goal of endoscopy is to determine the extent and location of the fungal infection in the pouch. If the plaque is restricted to the dorsocaudal aspect of the medial recess, then the internal carotid artery is the vessel of concern. If the fungal infection involves both lateral and medial recesses, then the branches of the external carotid are also at risk. Endoscopic examination inside the pouch is impossible if the horse is examined during or just after a hemorrhage. Endoscopy can confirm blood surrounding the nasopharyngeal opening of the guttural pouch, but examination of the interior of the pouch will need to be delayed. Usually 12 to 24 hours is a sufficient interval to permit enough clearance of blood so that viewing inside the pouch is possible.

A third goal of diagnosis is to determine whether one or both pouches are affected. Although isolated fungal lesions in each pouch are rare, a lesion that invades from the primary site through the medial septum into the other pouch is more common. Careful evaluation should also be made of the pharyngeal recess as mycotic lesions can erode from the guttural pouch into the nasopharynx at this location.

A fourth diagnostic goal is to thoroughly evaluate nasopharyngeal function. The soft palate is closely observed for signs of displacement or dysfunction during deglutition. If dysphagia or coughing has been noted, endoscopic examination of the trachea is warranted to assess potential feed contamination of the airways. The larynx is also evaluated for symmetry and normal function. Laryngeal hemiplegia can develop in spite of successful treatment of the mycotic infection. It is important that the owners are informed that preexisting neuromuscular dysfunction may not improve in spite of treatment. Modest improvement in pharyngeal function can continue for more than a year after resolution of the infection.

Radiographic evaluation of the guttural pouches can demonstrate a loss of air in the affected pouch if hemorrhage is present. Although rare, fungal lesions in the pouch

can invade osseous structures such as the stylohyoid bone or the atlantooccipital joint and this may be detected through radiography. Radiography and endoscopy are complementary and not mutually exclusive.

## Treatment

Treatment of guttural pouch mycosis is guided by its clinical presentation. Horses with a history of serious epistaxis are candidates for surgical intervention. Horses rarely die during the first episode of hemorrhage but more than 50% will die, usually within days to weeks, if they do not receive surgical treatment. Horses without a history of significant hemorrhage are treated surgically or medically or both. This author believes that if a fungal lesion is on an artery in the guttural pouch, surgical occlusion of the artery is the best treatment, regardless of whether hemorrhage has occurred or not.

Medical treatment of these lesions as the sole therapy is protracted and often unrewarding. Various medical and topical treatments (e.g., thiabendazole and povidone iodine) have been implemented over the years, but none have gained wide acceptance. This lack of acceptance is primarily the result of the fact that the repetitive treatments last for several weeks, and a fatal outcome accompanies therapy failure. Two case reports in the last 8 years detail resolution of guttural pouch mycosis (no history of hemorrhage) with specific antifungal therapy alone. In both cases systemic administration of itraconazole (5 mg/kg PO q24h for 3 weeks) was used. The two horses were also treated topically with endoscopic guidance. One horse received clotrimazole (1 g in 100 ml of polyethylene glycol weekly for 3 weeks). The lesion was resolved when examined at 4 weeks. The other horse was treated daily for 3 weeks with 60 ml of an aqueous solution of enilconazole (33.3 mg/ml). Additional work is needed to determine optimal dosages and strategies for improved contact between topical medications and the lesion. *A. fumigatus* and *nidulans* are opportunistic pathogens and require damage to the mucosal barrier to permit binding to fibrinogen on the mucosal surfaces. Another characteristic of these fungi is angiotropism. Resolution of mycotic plaques occurs after arterial thrombosis with no other treatment, regardless of whether the thrombosis occurs as a result of surgery or the disease. Until more clinical evidence is reported on the methods and efficacy of topical and systemic antifungal treatments, surgical intervention appears to be the more definitive treatment of fungal lesions associated with arteries of the guttural pouches. Medical treatment may well be indicated in the unusual horse where the mycotic plaque is clearly not associated with an artery.

Horses awaiting surgery should be fed and watered from an elevated position and kept very quiet to prevent a recurrence of epistaxis. Free access to drinking water and oral electrolytes should be provided, but intravenous fluids or blood transfusions are rarely indicated after the initial hemorrhage of a normovolemic horse. Blood pressure, packed cell volume, and plasma protein should be assessed and treated if signs of decompensation are evident. Acute interventions to reestablish normal circulating volume and blood pressure are contraindicated

because they may induce fatal hemorrhage by dislodging the arterial clot.

Surgical treatment of guttural pouch mycosis (GPM) is directed at occluding the affected artery. Surgical treatment of GPM was first accomplished by ligation of the internal carotid artery (the most commonly affected artery) on the cardiac side of the mycotic lesion. This technique does not prevent fatal hemorrhage from an artery with a transmural lesion because it does not prevent retrograde flow from the contralateral internal carotid artery through the intercarotid artery. Therefore the artery must be occluded on both sides of the mycotic lesion to prevent fatal retrograde hemorrhage. This requirement is true of the internal carotid artery as well as of any affected branches of the external carotid artery. Arterial ligation on the brain side of the lesion is not possible because of lack of surgical access and the lesion's proximity to the point at which the artery enters the skull.

The use of balloon-tipped catheters to occlude retrograde flow has been reported; complication rates of as high as 46% are related to the long indwelling catheter. Complications, most of which are not life-threatening, include incisional infection or catheter breakage. Detachable balloons have been used more recently and may be a good alternative. Embolization microcoils also can be placed into the affected artery as a means to bring about therapeutic occlusion. These microcoils have been used to occlude the internal carotid as well as the branches of the external carotid. The microcoils are commonly placed with the aid of dynamic fluoroscopy, although they can be placed with a technique similar to that used to place a balloon-tipped catheter. Contrast arteriography will confirm correct placement of the microcoils and occlusion of the intended artery. An affected artery with a transmural lesion is in contact with the nonsterile environment of the guttural pouch, therefore the passage of a catheter, contrast material, or flushing past the lesion has the potential to augment the flow of thrombi, bacteria, or fungi toward the brain. Although more than 30 clinical cases have been treated successfully with microcoil techniques,

this author has seen one horse develop neurologic signs 9 days after surgery. These signs were the result of a brain abscess caused by *S. equi*. Medical treatment failed. At other clinics, horses have died from brain infarcts following arterial occlusion operations as well as in nonoperated horses with guttural pouch mycosis.

Surgical treatment of hemorrhage from arterial wall mycotic lesions presents many technical challenges. Although the prognosis for survival can exceed 90% with surgical treatment, failures caused by aberrant vessel anatomy, extension of thrombi, or infection to the brain and persistence of cranial nerve dysfunction can be difficult to predict or prevent.

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## CHAPTER 7.8

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# Postanesthetic Upper Respiratory Tract Obstruction

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Upper respiratory tract (URT) obstruction can occur in horses recovering from general anesthesia after various surgical procedures. Postanesthetic URT obstruction most often results from nasal edema and/or congestion and is usually mild. Other causes include arytenoid chondritis, dorsal displacement of the soft palate, and bilateral arytenoid cartilage paralysis. Bilateral arytenoid cartilage paralysis is relatively uncommon; however, it can result in severe URT obstruction with the horse becoming distressed, uncontrollable, and difficult to treat. The condition may rapidly become fatal, thus postanesthetic URT obstruction can be a serious complication after general anesthesia and surgery.

### ETIOLOGY

#### Nasal Edema

Nasal edema and/or congestion is most often the result of venous congestion associated with a dependent head position during a prolonged anesthesia. Horses positioned in dorsal recumbency are thought to be more prone to nasal edema than horses in lateral recumbency. Nasal and pharyngeal edema may also result from trauma during endotracheal intubation that causes local inflammation and swelling.

#### Dorsal Displacement of the Soft Palate

Causes of dorsal displacement of the soft palate after extubation are unknown. The condition is most likely a normal consequence of orotracheal intubation and of administration of sedative and anesthetic drugs that alter URT neuromuscular function. If dorsal displacement persists, it is most likely the result of an underlying URT problem or of inflammation in the pharynx secondary to intubation.

#### Arytenoid Chondritis

Arytenoid chondritis is an uncommon cause of postanesthetic URT obstruction but can be a longer-term consequence of traumatic intubation. Although this condition will not lead to obstruction in the same anesthetic period, it may at a later time if it is not recognized. Furthermore, the presence of an abnormal arytenoid will compromise

the airway and can potentiate the possibility of an obstructive crisis.

#### Bilateral Laryngeal Paralysis

The etiology of postanesthetic bilateral laryngeal paralysis is unknown. Proposed etiologies include inflammation and edema of the larynx and neuromuscular failure. Physical trauma from endotracheal intubation or chemical irritation from residue after endotracheal tube cleaning may result in arytenoid chondritis, laryngeal dysfunction, and laryngeal inflammation and swelling. Laryngeal edema from venous congestion associated with a dependent head position during a prolonged anesthesia may cause swelling and failure of the arytenoid cartilages to adequately adduct. Causes of neuromuscular failure that lead to bilateral arytenoid cartilage paralysis include trauma to the cervical region or jugular vein; compression of the recurrent laryngeal nerve between the endotracheal tube or cuff and noncompliant neck structures; damage to the recurrent laryngeal nerve from intraoperative hypoxia, ischemia, or hypotension; and overextension of the neck when the horse is positioned in dorsal recumbency that causes damage to the recurrent laryngeal nerve as a result of compression of its blood supply.

$\alpha_2$ -Adrenergic agonists have been shown to increase laryngeal asynchrony and increase upper airway resistance in horses. The muscle relaxant effects of xylazine are thought to decrease the tone of the supporting airway muscles, which in combination with low head carriage may cause an increase in airway resistance. The muscle relaxant effects of xylazine may have worn off at the time the horse has recovered from anesthesia; however, one study showed that upper airway resistance increased for 30 to 40 minutes after xylazine administration and then slowly returned to normal. Impaired laryngeal function associated with xylazine administration in combination with excitement associated with recovery from anesthesia and extubation may lead to dynamic collapse of the upper respiratory tract and result in the clinical signs described. Xylazine is a commonly used preanesthetic drug; therefore although it is unlikely to be the sole cause of the URT obstruction, it may be a contributing factor.

Underlying URT disease such as laryngeal hemiplegia may also predispose horses to severe postanesthetic

obstruction. A few reports exist in the literature of severe postanesthetic URT obstruction in horses associated with laryngeal dysfunction. In two previous reports, bilateral arytenoid cartilage paralysis was associated with surgery in the head and neck region, and the horses recovered after establishment of a patent airway. These authors have recently seen several postanesthetic URT obstructions in horses that have undergone surgery for a variety of reasons including arthroscopy, tarsal arthrodesis, exploratory celiotomy, ovariohysterectomy, mastectomy, and prosthetic laryngoplasty/ventriculectomy. In addition to having undergone prosthetic laryngoplasty, some of these horses had a history of laryngeal hemiplegia before surgery. This fact suggests that preexisting disease may predispose to this condition. Postanesthetic URT obstruction in the horses at these authors' hospital is often associated with excitement or exertion, including standing after anesthesia and vocalization. The cause of severe obstruction therefore could be laryngospasm or dynamic adduction of both parietal arytenoid cartilages into the airway during inspiration.

In the horses at these authors' hospital, no association exists between difficult endotracheal intubation and URT obstruction. In horses that developed obstruction the duration of anesthesia was 90 to 240 minutes, and horses had mild-to-moderate hypotension, hypoventilation, and hypoxemia. These authors clean their endotracheal tubes with chlorhexidine gluconate between uses. If the tubes are not rinsed adequately, mucosal irritation from residual chlorhexidine gluconate could conceivably cause URT irritation and lead to obstruction. Most important, however, all these horses were positioned in dorsal recumbency for at least some of the time they were under anesthesia. The horses are positioned on a waterbed from the withers caudad. This position results in hyperextension of the neck and a dependent head position, both of which may predispose to postanesthetic bilateral arytenoid paralysis.

### Negative-Pressure Pulmonary Edema

Pulmonary edema can result from URT obstruction and has been referred to as *negative-pressure pulmonary edema* because the pulmonary edema occurs secondary to strong inspiratory efforts against a closed airway. In humans vigorous inspiratory efforts against a closed glottis may create a negative pressure of as low as  $-300$  mm Hg that, obeying Starling's laws of fluid dynamics, fluid moves from the intravascular space into the interstitium and alveoli.

### CLINICAL SIGNS

Although URT obstruction usually occurs immediately after extubation, severe obstruction associated with bilateral arytenoid paralysis may occur within 24 to 72 hours of recovery from anesthesia. The most obvious clinical sign is URT dyspnea. Horses with nasal edema have a loud inspiratory snoring noise, whereas horses with dorsal displacement of the soft palate have an inspiratory and expiratory snoring noise associated with fluttering of the soft palate. Horses with severe URT obstruction from bilateral laryngeal paralysis have a loud, high-pitched, inspiratory stridor associated with exaggerated inspiratory efforts.

## TREATMENT

### Nasal Edema

The most common type of upper respiratory tract obstruction is nasal edema, which often resolves rapidly without treatment. If obstruction is severe, it is critical to create a patent airway. The horse should be reintubated with a nasotracheal or orotracheal tube or 30-cm tubing placed in the nostrils to bypass the obstruction. Phenylephrine intranasal spray (5-10 mg in 10 ml water) or furosemide (1 mg/kg) may be used to reduce the nasal edema. Edema can be prevented by atraumatic intubation, reducing surgery time, and keeping the horse's head elevated during anesthesia and surgery.

### Dorsal Displacement of the Soft Palate

Dorsal displacement of the soft palate usually resolves spontaneously when the horse swallows, however, it may be corrected through induction of swallowing by gentle manipulation of the larynx or by insertion of a nasogastric tube into the pharynx.

### Bilateral Laryngeal Paralysis

Severe obstruction often develops when the horse stands after being extubated. Emergency treatment is required because the horse will rapidly become severely hypoxic, develop cardiovascular collapse, and die. Horses are often difficult to treat because obstruction may not be noticed until the horse is severely hypoxic and uncontrollable. Treatment is then delayed until the horse collapses from hypoxia, however, emergency reintubation or tracheostomy is often too late.

Immediate treatment consists of rapid reintubation or tracheostomy. Horses may be reintubated with a nasotracheal tube (14-22 mm) or an orotracheal tube (20-26 mm). The clinician performs a tracheostomy by clipping, preparing, and blocking the ventral cervical region (if time permits), making a 8-cm vertical incision on midline at the junction of the upper and middle thirds of the neck, bluntly separating the sternothyrohyoideus muscles, and then making a transverse incision between the tracheal rings. These authors recommend having a kit available with a tracheostomy tube and drugs for reinduction of anesthesia (xylazine, 1.1 mg/kg; ketamine, 2.2 mg/kg; or a paralytic agent such as succinylcholine, 330  $\mu$ g/kg IM). Horses should be treated with insufflation of oxygen immediately after establishment of an airway.

Prevention of URT obstruction after anesthesia requires treatment of hypotension, hypoxemia, and hypoventilation, avoidance hyperextension of the neck when horses are positioned in dorsal recumbency, and thorough rinsing of endotracheal tubes. These authors recover horses with the oral endotracheal tube in place, and following extubation closely monitor air movement.

If the horse has bilateral laryngeal paralysis, it may be necessary to establish a tracheostomy while the horse is treated aggressively with antiinflammatory treatment. Recovery should occur within days.

### Negative-Pressure Pulmonary Edema

Previous reports have described successful treatment of negative-pressure pulmonary edema, however, treatment may fail if a delay occurs between obstruction and treatment or if an unknown underlying disease is present. Treatment of negative-pressure pulmonary edema consists of administration of oxygen through nasal insufflation (10-15 L/min for an adult horse), a diuretic (furosemide, 1 mg/kg IV, and mannitol, 0.5-1.0 g/kg IV), antiinflammatory agents (flunixin meglumine, 1.1 mg/kg; dexamethasone, 0.1-0.3 mg/kg; dimethyl sulfoxide [DMSO]; 1 g/kg), and the positive inotrope epinephrine (2-5 µg/kg). Fluid therapy with polyionic isotonic fluids and electrolytes should be administered, however, overhydration of horses with pulmonary edema must be avoided.

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## CHAPTER 7.9

# Laser Surgery of the Upper Respiratory Tract

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**L**asers have become a common instrument for surgical and nonsurgical therapy in equine medicine. The many different tissue interactions that can be produced, the precision of its use, and the ability to apply laser energy to less accessible areas are the great advantages of the laser compared with other forms of therapy.

*Laser* is an acronym for *light amplification of stimulated emission of radiation*. The light emitted by lasers works according to the basic properties of light and electromagnetic radiation, but it is very different from the light produced by more common light sources such as incandescent bulbs, fluorescent lamps, or sunlight. The similarity between laser light and common white light is that all light consists of particles (photons) that travel through space in unique waveforms. White light consists of a mixture of many different wavelengths. Each color of visible light has its own characteristic wavelength. Visible light has an electromagnetic spectrum of wavelengths that range from approximately 400 nm to 700 nm.

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The components to create laser light are an active medium, a power source, an optical resonator, and an output coupler (partially transmitting mirror). The active medium is the material that determines the wavelength of the laser. The medium can be a gas, a liquid, a solid material, or a junction between two plates of semiconductor materials. The power source is the pump that stimulates the emission of radiation and the type of energy used as a power source is determined by the lasing medium. The optical resonator can be thought of as mirrors on either side of the medium that reflects the light back into the medium for "amplification." The output coupler allows a portion of the laser light contained between the two mirrors to leave the laser resonator in the form of a beam.

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### Negative-Pressure Pulmonary Edema

Previous reports have described successful treatment of negative-pressure pulmonary edema, however, treatment may fail if a delay occurs between obstruction and treatment or if an unknown underlying disease is present. Treatment of negative-pressure pulmonary edema consists of administration of oxygen through nasal insufflation (10-15 L/min for an adult horse), a diuretic (furosemide, 1 mg/kg IV, and mannitol, 0.5-1.0 g/kg IV), antiinflammatory agents (flunixin meglumine, 1.1 mg/kg; dexamethasone, 0.1-0.3 mg/kg; dimethyl sulfoxide [DMSO]; 1 g/kg), and the positive inotrope epinephrine (2-5  $\mu$ g/kg). Fluid therapy with polyionic isotonic fluids and electrolytes should be administered, however, overhydration of horses with pulmonary edema must be avoided.

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## CHAPTER 7.9

# Laser Surgery of the Upper Respiratory Tract

ERIC J. PARENTE

*Kennett Square, Pennsylvania*

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size ( $\text{W}/\text{cm}^2$ ). Therefore a larger beam size of a given power will have a smaller irradiance. The number of joules depicts the total energy, which is equal to the laser output (watts) multiplied by the exposure time (seconds). The "energy fluence" is equal to joules/laser beam size, and measures the total amount of energy directed to the tissue during a treatment. An understanding of this fact is important because the effectiveness of a particular laser is determined not only by its wavelength but also by how it is used.

Laser light interacts with tissue in several ways. It can be absorbed, transmitted, reflected, or scattered. The percentage of each interaction is dependent on the characteristics of the tissue and the laser light. The amount of absorption is dependent on the wavelength of the light relative to the chromophore content of the tissue (hemoglobin, keratin, protein, water, melanin). Each chromophore has its own absorption spectrum for different wavelengths of light. If the light is absorbed it is transformed into heat energy. Heating tissue to  $60^\circ\text{C}$  will lead to coagulation of proteins, and heating tissue to higher than  $100^\circ\text{C}$  will result in vaporization. Thus lasers will yield different biologic effects dependent on the energy absorption coefficient. Although vaporization and coagulation can be seen at the time of surgery, a zone of thermal injury exists beyond what can be seen at surgery. If a large amount of energy is expended that is not strictly focused on the area of interest, excessive swelling and trauma to the tissues may occur postoperatively.

## THERAPEUTIC LASERS

Lasers have become a common tool to speed healing in many different types of injuries. The lasers used for this purpose differ greatly from surgical lasers. Therapeutic lasers are considered "cold" or low-power lasers and fall into classes II and III. They may induce some heat but no greater than that which would be felt from a 60-W bulb held close to the skin. The benefits of these lasers are the analgesic effects caused by alterations in nerve conduction and wound healing caused by stimulation of changes in intracellular calcium that ultimately results in increased protein synthesis and collagen production. The most common lasers employed are the gallium arsenide (GaAs) and helium neon (HeNe) lasers at a distance of 1 to 2 mm from the surface of the target tissue for a total energy density of  $5\text{ J}/\text{cm}^2$ .

## SURGICAL LASERS

Although surgical lasers have existed since 1960, it was not until lasers could be applied through small flexible fibers that these tools had an enormous impact on equine surgery. These fibers can be passed down the biopsy channel of a videoendoscope and employed under videoendoscopic control. This development revolutionized the treatment of upper respiratory conditions by providing the surgeon an opportunity to approach lesions within the nasal cavity, larynx, and pharynx without making a surgical skin incision. This new procedure also provided a technique for cutting a fairly reactive and very well-vascularized tissue that is precise and provides significant hemostasis.

The two most common lasers used for upper respiratory surgery are the diode and Nd:YAG lasers. They have wavelengths of 980 nm and 1064 nm, respectively, and can pass down a small flexible optical quartz fiber without significant disruption of wavelength. The diode laser has two main advantages compared with the Nd:YAG. The diode laser is a much smaller unit (less than 15 lb) and is significantly less expensive than the Nd:YAG. The major disadvantage of the diode laser is its power limitation of 25 W, whereas the Nd:YAG can exceed 50 W. Other lasers such as the  $\text{CO}_2$  cannot pass down a small fiber effectively because of their much larger wavelength and therefore cannot be used with a standard videoendoscope. Although the  $\text{CO}_2$  laser wavelength is strongly absorbed by water and therefore is an excellent precise cutter, it has only poor-to-fair coagulating capability. The diode or Nd:YAG wavelengths are diffusely absorbed by all protein molecules and therefore have greater coagulation capabilities, although they do not cut as well as the  $\text{CO}_2$  laser.

The laser can be used in contact or noncontact mode. Most surgeries can be performed with a bare fiber (no special tip) in contact mode. This method provides very accurate, controlled cutting and hemostasis of the small vessels in the respiratory mucosa, and provides the surgeon some tactile sense of the procedure. A lower power setting of 14 to 18 W is sufficient in most cases. This also means that a small very portable diode laser can be employed. If the laser is used correctly, little lateral thermal damage should occur. The surgeon resects the tissue by dragging the fiber across the tissue as he or she would lightly drag a scalpel blade. The types of surgeries commonly done in this fashion include axial division of epiglottic entrapment, resection of subepiglottic or pharyngeal cysts, vocal cord resections, resection of granulation tissue, and treatment of guttural pouch tympanites.

With noncontact laser surgery, the fiber is held 3 to 5 mm away from the target tissue. A higher power setting of 40 to 60 W is commonly required to work effectively, which requires an Nd:YAG laser. Noncontact surgery is used mostly for ablation of cystlike structures such as ethmoid hematomas or pharyngeal cysts and to vaporize membranous structures.

## GENERAL USE

A great advantage of the use of lasers in respiratory surgery is that many of the surgeries can be done on the standing, sedated animal on an outpatient basis. This fact also equates to a shorter, easier postoperative management because no skin incision is present. Procedures can be performed with the animal standing in the stocks with just intravenous sedation such as xylazine ( $0.44\text{ mg}/\text{kg}$ ). Repeated half doses or a longer-acting agent may be required depending on the procedure and the experience of the surgeon. With the horse sedated, a twitch is normally not required to pass the endoscope. The horse's head can be suspended from cross ties for support, but an individual must always be positioned at the horse's head for safety and to alter the head position as needed. Topical anesthetic is applied to the area of interest through polyethylene tubing that is advanced down the biopsy channel of the endoscope. The horse often swallows while the anes-

thetic is applied, and application should be intermittently suspended to make certain the anesthetic is applied appropriately in between swallows. The anesthetic is usually effective for approximately 2 hours, so the animal is not allowed to eat for 1 to 2 hours after surgery.

Laser safety should always be considered. Although the laser is used within the respiratory cavity, surgical personnel should still wear laser safety glasses as a precaution against any misfiring of the laser. The laser should always be kept in the standby mode when not being used. If a procedure is performed with the horse under general anesthesia near an endotracheal tube, the oxygen concentration should be decreased with helium to dramatically reduce the risk of spontaneous ignition. Smoke evacuation is usually not necessary in contact laser surgery in the standing horse but may be required in noncontact work or when the horse is under general anesthesia.

Antiinflammatory medication is the cornerstone of postoperative management in the upper respiratory tract. Phenylbutazone (4.4 mg/kg) and dexamethasone (0.044 mg/kg) are given in the immediate postoperative period. Both medications are recommended for several days at a decreased dose depending on the type of surgery and anticipated degree of inflammation. Local antiinflammatory medication can also be administered through a 10-Fr catheter that is advanced through the nasal passage into the nasopharynx. Ten milliliters of a mixture of dimethyl sulfoxide, glycerine, and dexamethasone solution are administered slowly through the catheter while watching the horse swallow. This mixture is administered twice daily for as long as 7 days.

Antimicrobials are not commonly given unless the surgeon is working on areas of thickened scar tissue where the vascularity may be compromised, or extensive use of the laser is required. Although vaporization of all tissue with the laser results in a sterile incision, the adjacent tissues of the throat and mouth can easily contaminate the open wound bed at the conclusion of surgery. Surgical inexperience can lead to greater thermal injury than visually appreciated and increased susceptibility to infection even in healthy tissues, particularly when the laser is used on subepiglottic tissues.

## COMMON PROCEDURES

### Axial Division of Epiglottic Entrapment

Almost all entrapments are amenable to surgery with the laser in contact fashion with the exception of the most severely thickened, chronic cases. The horse is sedated as described previously. The topical anesthetic is applied to the entrapping membrane and to the dorsal surface of the epiglottis. The laser is set to 16 W. The laser fiber is extended 1 to 2 cm beyond the endoscope so the plastic sheath around the optical fiber can be clearly seen. To perform the cut, the fiber is dragged rostrally on dorsal midline beginning at the caudal edge of the entrapping membrane toward the tip of the epiglottis. Before engaging the laser in this manner, the surgeon should ensure that the laser fiber will maintain contact with the tissue through the entire stroke of the maneuver. Sometimes an alteration in the horse's head position is required. The membrane

will peel back with each stroke and it will require multiple strokes to cut entirely through the membrane before it is released from the epiglottis. When the cut is almost complete swallowing can be induced, which will pull the membranes ventrally. If the membrane recedes completely under the epiglottis the horse is induced to swallow again to guarantee that the entrapment does not return. If the entrapment does not return after multiple swallows, the procedure is complete. Usually it requires 1000 to 3000 J to perform the entire procedure. The horse is treated with antiinflammatories as described, and after 2 to 3 weeks of rest the horse can resume exercise. Antimicrobials are not necessary in the simplest entrapments. Ulcerated entrapments are treated similarly. Antimicrobials are recommended for entrapments that have a very thickened membrane. If after the division is complete the membranes do not recede under the epiglottis, horses should be initially treated medically and entrapment should resolve within 7 to 10 days. If membranes persist in an abnormal position, the surgeon can grab them with a 600 mm long bronchoesophageal grasping forceps and resect them with the laser in contact fashion.

### Cysts

Cysts can occur on the wall of the pharynx or in the subepiglottic region. Pharyngeal cysts commonly appear on the dorsal surface of the pharynx and can be easily resected by using the laser in contact fashion. In this approach, the surgeon strokes the fiber across the junction of the cyst with the pharyngeal wall. The cystic tissue can be grasped through a long grasping forceps that enters through the opposite nostril. An alternative method would be to vaporize the cyst with the laser in noncontact fashion. The fiber with a power setting of 40 W is held perpendicular and just millimeters away from the cyst. The surgeon slowly blanches the cyst with a sweeping motion of the fiber over the cyst without puncturing it until complete vaporization occurs.

Subepiglottic cysts are more challenging. If the cyst can be seen above the palate, the horse can be sedated and the area anesthetized as described. Care should be taken not to cause the horse to swallow once the throat is anesthetized until the cyst is firmly grasped with the grasping forceps. If the cyst falls back under the palate it will be difficult to get it above again. Once the cyst is grasped with rotation of the forceps and some traction or repulsion, the base of the cyst can be brought into view and resected with the laser fiber in contact fashion. The cyst may be accidentally punctured during the procedure, but the abnormal membrane can still be seen and resected. If the cyst cannot be managed above the palate, it is recommended that the horse be placed under general anesthesia and the procedure be performed similarly but through the horse's mouth. Suction may be required for smoke evacuation. One week of antiinflammatory medication and 3 weeks of rest are recommended before the horse returns to exercise.

### Arytenoid Granulation Tissue

Removal with the laser can be an effective treatment for granulation tissue in the absence of significant underlying



pathologic process of the arytenoid or continued trauma to the arytenoid secondary to hemiplegia. The horse is sedated and locally anesthetized as described previously. Noncontact laser ablation would likely result in too much unappreciated thermal damage, so contact laser excision is recommended. The surgeon drags the fiber across the base of the granulation tissue until it is almost completely loose before attempting to grasp it. Once it is grasped, just one to two more passes should release the tissue for removal. If the surgeon grasps the tissue early in the procedure, shredding of the tissue will occur along with a great deal of swallowing in the horse.

### Chordectomy

This procedure is always done as an adjunct to a laryngoplasty or alone in cases of more mild hemiplegia in non-racehorses. Chordectomy is easiest to perform with the horse under general anesthesia with a contact laser, but it can be done with the horse standing.

The horse is placed under general anesthesia with the vocal cord to be resected uppermost and the horse is then nasotracheally intubated. Oxygen concentration is decreased with helium to prevent ignition of the gases within the endotracheal tube. A speculum is placed in the horse's mouth and suction tubing is manually placed just rostral to the down vocal cord. Bronchoesophageal forceps are placed through the horse's mouth with the video endoscope and the targeted vocal cord is grasped. If it cannot be grasped because of the vertical orientation of the cord and the jaws, an initial cut is made through the cord with the laser just below the vocal process. This procedure results in a horizontal plane of tissue that can be grasped. The forceps are rotated to place tension on the cord away from the sacculle, and the fiber is used to cut from dorsal to

ventral. Once the most ventral aspect of the cord is reached the forceps are derotated to separate the cords slightly; the targeted cord is then repelled caudally. This method allows the surgeon to observe any tension on the medial side of the cord so it can be transected, freeing the cord entirely for removal. A 4 × 4 gauze sponge tied to 40 cm of umbilical tape can be placed in the defect to provide hemostasis while the laryngoplasty proceeds. The gauze is removed just before the horse enters the recovery stall.

### CONCLUSION

Although the laser has become an invaluable tool for many upper respiratory surgeries, its improper use can create significant trauma and irreparable damage. Great care should be taken to use only as much energy as necessary to complete the task and minimize extraneous firing. When used appropriately, the laser greatly diminishes the need for more extensive surgery and speeds the recovery of the patient.

### Supplemental Readings

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## CHAPTER 7.10

# Permanent Tracheostomy in Standing Horses

PETER C. RAKESTRAW  
*College Station, Texas*

**D**iseases of the upper airway such as laryngeal hemiplegia, arytenoid chondritis, subepiglottic cysts, aryepiglottic fold entrapment, and dorsal displacement of the soft palate are commonly encountered in horses. In all of these conditions some abnormality of the upper airway compromises the cross-sectional area of the airway and causes decreased airflow; the condition usually becomes clinically significant only at exercise. In the majority of these cases, surgical correction

specifically addresses the area of compromise and corrects the abnormality.

Certain conditions exist, however, in which the lesion causes such severe stenosis of the upper airway that surgical correction of the lesion is met with a guarded or poor long-term prognosis. In this author's experience and based on literature review, the most common conditions in which less invasive procedures have failed are related to the problem of nasopharyngeal cicatrix. In this syndrome,

pathologic process of the arytenoid or continued trauma to the arytenoid secondary to hemiplegia. The horse is sedated and locally anesthetized as described previously. Noncontact laser ablation would likely result in too much unappreciated thermal damage, so contact laser excision is recommended. The surgeon drags the fiber across the base of the granulation tissue until it is almost completely loose before attempting to grasp it. Once it is grasped, just one to two more passes should release the tissue for removal. If the surgeon grasps the tissue early in the procedure, shredding of the tissue will occur along with a great deal of swallowing in the horse.

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a circular web of tissue forms in the pharynx, first ventrally over the floor of the pharynx and then dorsally, in which position it extends above the pharyngeal openings of the guttural pouches. Arytenoid chondritis is commonly associated with this generalized inflammatory process. Resection of the diseased cartilage does not seem to be curative because the generalized inflammatory process continues with the subsequent pharyngeal/laryngeal swelling that leads to obstruction of the airway. In these cases, permanent tracheostomy can provide an effective alternative approach by bypassing the obstruction. Other indications for a permanent tracheostomy are neoplasia of the upper airway and severe deformity of the nasal passages.

## SURGICAL TECHNIQUE

Although permanent tracheostomy can be performed with the horse under general anesthesia, the technique described here can be readily performed in the standing horse. This provides some advantages because the surgical structures are in a more normal anatomic orientation and create less tension on the tracheostomy closure during the healing period. This position also avoids complications associated with general anesthesia and recovery and reduces the expense of the procedure.

Perioperative antibiotics (procaine penicillin G, 20,000 IU/kg q12h, IM) and antiinflammatories (flunixin meglumine, 1.1 mg/kg IV) should be administered. The horse is restrained in the stocks and cross-tied so that it is positioned forward in the stocks with its head extended in front of the side poles of the stocks. With this restraint, the surgeon has easy access to the surgical area. Maintenance of this position is easier if the horse's head is suspended from a bar that extends from the top of the stocks over the head. The head is suspended by means of the halter that is placed upside down so that the throat-latch strap is over the horse's forehead (between the eyes and ears) and not under the throat adjacent to the surgical site. Padding should be placed between the halter and the mandible to prevent facial nerve paralysis. Placement of the horse's head in a stand similar to a crutch may also help in maintaining the head and neck in an extended position. Sedation and analgesia is provided by administration of detomidine (0.02 mg/kg, half administered IV and half IM) and butorphanol (0.011 to 0.022 mg/kg IV).

The incision is positioned over the second to sixth tracheal rings. Local anesthesia is infiltrated subcutaneously in an inverted U pattern dorsal and lateral to the second through sixth tracheal rings. Starting approximately 3 cm distal to the cricoid cartilage and centered over midline, the surgeon removes a 3-cm wide  $\times$  6-cm long rectangular section of skin. The surgeon then continues the incision on midline, separating the paired sternothyrohyoid muscles to expose the tracheal rings. Dissection is performed laterally around the abaxial borders of the paired sternothyrohyoid muscle. The muscle bellies are isolated and clamped (Ferguson Angiotribe Forceps; Miltex, Lake Success, N.Y.) at their proximal and distal exposure in the incision. After clamping for several minutes to crush the vessels, the muscle bellies are transected. This author also recommends removal of a section of the omohyoid muscle in a similar fashion. The fascia covering the tracheal rings is carefully removed. A ventral midline inci-

sion and two paramedian incisions, approximately 15 mm on either side of the midline incision, are made through the tracheal ring cartilage without penetrating the tracheal mucosa. The tracheal cartilage segments are carefully dissected free from the tracheal submucosa, leaving the submucosa and mucosa intact. Although this may appear very difficult, the mucosa is thick and separates easily from the rings with patient dissection.

Most commonly a total of five tracheal rings (two through six) are removed although removal of four rings is often adequate. To alleviate dead space, subcutaneous tissue is sutured to the tracheal fascia with 0-polydioxane (PDS; Ethicon Inc, Somerville, N.J.) with use of a simple interrupted pattern. In some horses this author inserts a 23-gauge, 2.5-cm needle into the lumen of the trachea and injects 30 ml of 2.5% lidocaine HCl proximal to the incision to desensitize the tracheal mucosa. The tracheal mucosa is incised in what has been described as a *double Y* pattern. In this pattern, a central midline incision is made that ends approximately one tracheal ring width before the rostral and caudal ends of exposed tracheal mucosa. The midline incision is extended as a V with each leg connecting to the corners of one end of the exposed rectangular section of tracheal mucosa. In this way, a double Y pattern is formed. The surgeon sutures the tracheal mucosa and submucosa to the skin with simple interrupted sutures of 0-polydioxane, starting at the ends and then suturing along the lateral borders.

## AFTERCARE

Because the proximal trachea is not a sterile environment, antibiotics should be administered for 5 to 7 days postoperatively. Nonsteroidal antiinflammatory drugs should be continued for 5 to 7 days depending on the amount of postoperative swelling. The stoma should be cleaned once or twice daily until the sutures are removed 10 to 14 days after surgery. The stoma needs to be cleaned daily for the first month after surgery, but usually by 1 to 2 months postoperatively the discharge will decrease and make daily cleaning unnecessary. In the majority of this author's long-term postoperative cases, cleaning has been necessary only once or twice a week.

In this author's experience, postoperative swelling with or without partial dehiscence is the most commonly encountered complication. Incisions that develop partial dehiscence can heal satisfactorily by second intention. In some cases the areas of partial dehiscence have had to be surgically repaired, a method that usually involves removing more of the adjacent muscle and resuturing the mucosa and submucosa to the skin. In a small percentage of cases that had insufficient stoma size repairs were made by removing sections of the omohyoid muscle. Because of this experience, this author now routinely removes a portion of the omohyoid when performing a tracheostomy.

## PROGNOSIS

In this author's experience the long-term prognosis after tracheostomy is good, and more than 90% of owners say that they are pleased with the outcome. Tracheostomy has been performed on many broodmares without causing problems during foaling, although close observation of the mare around the foaling period is still recommended. In

some horses the tracheostomies were performed more than 10 years ago and the stoma is still patent and causes no problems. This procedure does not prevent the horse from being used for athletic purposes; some of the aforementioned horses are used for pleasure riding and some used as Western performance horses. Although the tracheostomy bypasses a component of the pulmonary defense mechanism that acts to moderate temperature and humidity and filter inspired air, these horses have not appeared to be predisposed to airway infections. Approximately one fourth cough occasionally during exercise, most likely because of irritation of the trachea from dust particles. Consequently maintenance of the horses in an environment that is as dust-free as possible is recommended.

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## CHAPTER 7.11

# Medical Treatment of Upper Airway Dysfunction

SUSAN J. HOLCOMBE

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For some practitioners, medical management of dynamic obstructive nasopharyngeal diseases has transcended surgical therapy and become a more popular and effective method to treat and manage a number of upper respiratory tract disorders in performance horses. Inflammation subsequent to viral or bacterial infections may be the inciting cause of some of these obstructive diseases. In these instances, medical treatment of upper respiratory disease is warranted and may include corticosteroids, antimicrobial therapy, nonsteroidal antiinflammatory drugs, and topical or aerosolized therapies.

### INFLAMMATORY UPPER AIRWAY DISEASE AND MUSCLE DYSFUNCTION

Inflammation and infection of the upper airway may affect the innervation of the dilating muscles of the upper airway and result in muscle dysfunction and airway obstruction. These same muscles are also used during swallowing. Many of the nerves that innervate these muscles pass through or immediately adjacent to the guttural pouches and/or are closely associated with the dorsal wall of the nasopharynx. During bouts of severe inflammation caused by conditions such as empyema or guttural pouch mycosis these regions can become severely inflamed, resulting in dysphagia. Because similar muscles used in swallowing also function to dilate and stabilize the nasophar-

ynx during breathing, it is quite likely that less severe inflammation of the upper airway such as pharyngitis may cause dysfunction of the same neuromuscular groups and result in dynamic airway obstruction during exercise.

Severe inflammation within the guttural pouch can be a result of empyema, fungal infections, or caustic infusions such as iodine. Inflammation can also accompany *Streptococcus equi* abscessation of retropharyngeal lymph nodes. This severe inflammation can cause dysphagia, which is accompanied by nasopharyngeal airway collapse. Collapse occurs because the nerves controlling the pharyngeal muscles, specifically branches of the vagus and glossopharyngeal nerves, are detrimentally affected by the infection. Clinically, the flaccidity of the nasopharynx is less noticeable because the dysphagia is relatively dramatic and these horses are seldom exercised. Frequently, dysphagic horses have persistent or permanent dorsal displacement of the soft palate. Microscopic study of pertinent cranial nerves in affected horses has revealed active neuritis. Lesions range from slight swelling of myelin sheaths and Schwann cells with dilation of intraneural capillaries to heavy leukocytic infiltration of the nerves and necrosis.

Experimentally, persistent soft palate displacement can be induced by anesthetizing the pharyngeal branches of the vagus nerves, bilaterally. Microscopic lesions of the cranial nerves qualitatively similar to those

some horses the tracheostomies were performed more than 10 years ago and the stoma is still patent and causes no problems. This procedure does not prevent the horse from being used for athletic purposes; some of the aforementioned horses are used for pleasure riding and some used as Western performance horses. Although the tracheostomy bypasses a component of the pulmonary defense mechanism that acts to moderate temperature and humidity and filter inspired air, these horses have not appeared to be predisposed to airway infections. Approximately one fourth cough occasionally during exercise, most likely because of irritation of the trachea from dust particles. Consequently maintenance of the horses in an environment that is as dust-free as possible is recommended.

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Experimentally, persistent soft palate displacement can be induced by anesthetizing the pharyngeal branches of the vagus nerves, bilaterally. Microscopic lesions of the cranial nerves qualitatively similar to those

seen in dysphagic horses have been observed in horses with intermittent dorsal displacement of the soft palate. Specifically, right and left sections of the pharyngeal branch of the vagus nerve had mild multifocal myelin degeneration. Cranial nerve lesions that cause upper airway or nasopharyngeal dysfunction are potentially reversible, as demonstrated by observations of horses with guttural pouch mycosis. In a group of affected horses, approximately 50% of horses with pharyngeal paralysis and dysphagia recovered within 4 to 6 months after combined medical and surgical therapy for the mycotic infection. This recovery suggests that the pharyngeal paresis was caused by reversible neurapraxia. It seems reasonable to conclude that a number of the dynamic obstructive diseases of the equine nasopharynx can be effectively treated with early, aggressive antiinflammatory therapy.

### **PHARYNGEAL LYMPHOID HYPERPLASIA: NORMAL ADAPTATION OR PRELUDE TO OBSTRUCTIVE AIRWAY DISEASE?**

Horses (especially young horses) frequently have upper airway inflammation characterized by edema, erythema, and nasopharyngeal lymphoid hyperplasia. Upper airway inflammation and pharyngeal lymphoid hyperplasia have been associated with viral diseases, environmental antigens, and bacterial infections. Horses with these conditions frequently have concurrent guttural pouch inflammation, manifested by edema, erythema, accumulations of exudate, lymphoid follicular hyperplasia within the guttural pouch lining, and enlarged retropharyngeal lymph nodes on the ventral floor of the medial compartment.

Conflicting evidence exists as to the effect of pharyngeal lymphoid hyperplasia on racing performance and thus as to whether or not treatment is warranted. In one study 68 of 70 young Thoroughbred racehorses had evidence of pharyngeal lymphoid hyperplasia or pharyngitis; the severity of the inflammation decreased with age. In addition, 2-year-old horses had the most severe inflammation when compared with other age groups. In this study none of the horses had a history of diminished racing performance. These results suggest that pharyngeal lymphoid hyperplasia may be a normal response to environmental antigens. Therefore because pharyngitis is frequently self-limiting and has not been definitively associated with poor performance, this disease is usually not treated. However, the sequel of nasopharyngeal inflammation may be more performance-limiting than the initial bout of pharyngitis. Accumulating evidence suggests that regional inflammation of the upper airway may be responsible for some obstructive upper airway disease, such as nasopharyngeal collapse and dorsal displacement of the soft palate.

### **MEDICAL THERAPY FOR UPPER AIRWAY DISEASE**

Because of the possibility that regional inflammation of the upper airway may be responsible for some obstructive upper airway diseases, enteral, parenteral, and topical antiin-

flammatory therapy may prove useful in their treatment. Although a proven correlation between airway inflammation and upper airway obstructive diseases remains to be established, an association exists between the presence of upper airway inflammation and the occurrence of obstructive upper airway disease. This premise finds support in numerous anecdotal accounts of improved upper airway function in horses after antiinflammatory treatment.

Systemic and inhaled corticosteroids have been used successfully to treat upper airway inflammation and neuromuscular dysfunction that results in dorsal and lateral nasopharyngeal collapse and dorsal displacement of the soft palate. After a thorough physical examination and complete blood cell count and fibrinogen have been performed to rule out active bacterial infection, systemic corticosteroid therapy can be initiated. Dexamethasone can be administered in a tapering dose, orally, at 0.02 to 0.04 mg/kg twice daily for 10 days to 2 weeks, followed by 0.02 to 0.04 mg/kg, once daily for 10 days to 2 weeks, then 0.02 to 0.04 mg/kg every other day for 2 weeks. The horse should be rested during this time, and either turned out in a pasture or worked lightly for 6 to 8 weeks. The airway inflammation typically resolves within 7 to 10 days, however, upper airway function may not improve for as long as 4 months, thus patience is important. Oral prednisolone can also be given at 1 to 2 mg/kg with the same dosing regimen as dexamethasone. It is important to note that oral prednisone therapy in horses is ineffective. Prednisone is poorly absorbed by the equine gastrointestinal tract and is not converted to the active antiinflammatory form, prednisolone.

Inhaled and topical medications have also been used to decrease airway inflammation in horses. Dexamethasone and prednisolone can be nebulized for distribution in the nasopharynx. Antiinflammatory topical throat sprays, composed of nitrofurazone, dimethyl sulfoxide, glycerin, and prednisolone or dexamethasone, can be administered into the nasopharynx by passing a uterine infusion pipette or narrowing tubing of sufficient length into the nasopharynx and spraying 10 to 20 ml of the solution into the nasopharynx. Application of throat spray may be performed twice daily for 2 weeks and then daily for 2 weeks.

Interferons are a family of proteins that have antiviral and immunomodulatory activity. Oral administration of a low dose (0.1 IU/kg) of human interferon- $\alpha$  (HuIFN $\alpha$ ) reduces tracheal and nasopharyngeal exudate in racehorses with inflammatory airway disease. Horses are generally treated daily for 5 to 7 days. Oral administration of HuIFN $\alpha$  likely is effective because it stimulates lymphoid tissue in the oropharynx. At Michigan State University the following procedure is used to prepare interferon:

1. Add 1 ml of interferon  $\alpha$ -2a (3 million U/ml, Roferon-A) to 99 ml of 0.9% saline and mix well but do not shake. This makes 100 ml of 30,000 U/ml interferon  $\alpha$ -2a.
2. Remove 143 ml of 0.9% saline from a 1-L container and add 3 ml of the 30,000 U/ml interferon  $\alpha$ -2a solution. The final volume of 900 ml will contain 100 U/ml interferon  $\alpha$ -2a.

3. Divide the 100 U/ml solution into aliquots of 30 ml each, place in 1 oz bottles, and refrigerate.
4. Label each aliquot with the following information:
  - Interferon  $\alpha$ -2a 100 U/ml.
  - Store in refrigerator.
  - Prepared on date \_\_\_\_ .
  - Discard after 30 days.

Discard any solution remaining from step 1. Interferon tends to bind to surfaces and any long-term storage must be in a  $-70^{\circ}\text{C}$  freezer.

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# SECTION VIII

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## Respiratory Diseases

*Edited by Dr. Andrew M. Hoffman*

### CHAPTER 8.1

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## Tracheal Aspirates: Indications, Technique, and Interpretation

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**E**valuation of respiratory tract disorders in horses has evolved over recent years: a number of new techniques and modifications of existing techniques have been developed. Current methods allow greater precision for assessment of the lower respiratory tract, but some confusion remains regarding the indications for the various techniques and the interpretation of results obtained.

Aspirates from the trachea commonly are used in equine medicine to evaluate individuals with suspected respiratory disease. The transtracheal method was introduced to allow collection of uncontaminated material from the lower respiratory tract for bacterial culture, in addition to secretions for cytologic assessment. More recently, collection of samples using a fiberoptic endoscope, with either a nonguarded or guarded catheter, has become routine.

#### INDICATIONS

An accurate diagnosis of the underlying disorder is a prerequisite for successful management of equine respiratory tract disease. The techniques used to determine this diagnosis may vary between cases, but a thorough physical examination and careful auscultation always should be performed. These may be sufficiently characteristic for a diagnosis or may indicate the need for further testing. Several key features of the history and clinical examination provide strong indications for collection of samples from the lower respiratory tract. These include coughing (especially during exercise), nasal discharge, persistent tachypnea, dyspnea, fever, poor performance, and exercise intolerance.

Endoscopic findings of increased amounts of mucus and/or mucopurulent exudate are an additional indication for investigation of the nature of these secretions.

#### Tracheal Aspirate or Bronchoalveolar Lavage?

The choice of diagnostic techniques for evaluation of the respiratory tract is influenced by a number of factors including the history and presenting signs, likely differential diagnoses, ease of technique, and use of the horse (e.g., performance versus pleasure). However, these techniques are not interchangeable, and misinterpretation of results is likely if this assumption is made. Tracheal aspirates (TA) and bronchoalveolar lavage (BAL) sample different areas of the lung. The TA samples discharges that pool in the trachea from anywhere in the lung, and BAL samples a region of peripheral lung. Use of the latter assumes that lung disease is diffuse or that the specific diseased region can be identified and sampled. Furthermore, no significant correlation between TA and BAL cytology has been found. Therefore in terms of inflammation the respiratory system may be "compartmentalized." Consequently, an increased number of inflammatory cells may be present in a TA but not a BAL, and vice versa. A "healthy" sample obtained by either of these techniques does not necessarily indicate absence of disease in the entire lung.

In some cases, in which a specific diagnosis has a high degree of certainty based on history and clinical signs, one or the other of these techniques may be indicated; for example, BAL in cases of suspected heaves or exercise-induced pulmonary hemorrhage (EIPH), or TA in cases of



suspected bacterial pneumonia or pleuropneumonia. In other situations in which the diagnosis is unresolved, such as cases of poor performance or coughing during exercise, collection of both samples concurrently is indicated to assess the overall health of the airways.

## TECHNIQUE

Several methods for obtaining TAs have been developed, each having advantages and disadvantages. The most important consideration when choosing a technique is whether microbiologic culture of the tracheobronchial secretions is indicated. In general, aspirates obtained endoscopically are unsuitable for this use because they invariably become contaminated by upper airway flora. However, a guarded catheter passed through the endoscope may be used to obtain samples suitable for microbiologic culture. Alternatively, the transtracheal (percutaneous) aspiration technique may be employed.

The choice of technique can affect significantly the numbers and types of cells obtained. Thus standardization of procedures with regard to type of technique, time of sampling, volume and type of fluid instilled, sample handling, and processing is recommended for meaningful interpretation and comparison of results.

### Transtracheal Aspirates

The rationale for use of transtracheal aspiration is based on the assumption that the bacterial population derived from the upper airway of normal horses is negligible beyond the proximal trachea. Therefore organisms cultivated from a TA represent bacteria found in the distal trachea and lower airways. These bacteria may be present transiently, or they may be part of a pathologic process. The distinction between these phenomena is important.

Samples obtained by transtracheal aspiration are suitable for cytologic and Gram's stain evaluation and bacteriologic or fungal cultivation. However, this technique is invasive, and possible complications have tended to preclude its widespread application. These include subcutaneous abscessation at the puncture site, tracheal laceration and hemorrhage, chondritis, and pneumomediastinum. In addition, the catheter may break off in the tracheal lumen, although in most cases it is coughed up rapidly and swallowed. Good technique prevents most untoward complications.

A variety of needle-catheter combinations may be used, but maintaining asepsis is critical. The components may be purchased either individually or prepackaged and include an introducer catheter-over-needle, flushing catheter, and a stylet (Catheter TW 1228 and 1628, Mila International, Phoenix, Ariz.). A convenient combination of catheters comprises a 12-gauge needle, 3-inch over-the-needle cannula, and number 5 French canine urinary catheter with the tip cut off obliquely.

Sedation generally is indicated when performing a tracheal aspiration, with xylazine (Rompun) used commonly. An area measuring approximately 6 by 6 cm over the middle third of the cervical trachea should be clipped and prepared for aseptic surgery. A bleb of local anaesthetic (approximately 1 ml) is injected subcutaneously over the

midline and a stab incision is made through the skin and subcutaneous tissue with a number 15-scalpel blade. The trachea is stabilized with one hand and the cannula is introduced into the tracheal lumen between two cartilage rings. The stylet is removed, and the urinary catheter is passed down into the tracheal lumen to the level of the thoracic inlet, where the washing and aspiration is performed. In most cases 10 to 15 ml of sterile isotonic saline is adequate to obtain a satisfactory sample. However, repeated infusions may be required. Once an adequate sample has been collected, the catheter should be withdrawn, maintaining the cannula *in situ* during retraction to minimize contamination of peritracheal tissues.

### Tracheal Aspirates: Endoscopic Technique Using Unguarded Catheters

An increasingly popular and well-tolerated alternative for collection of TAs is via a fiberoptic endoscope. However, samples collected using unguarded catheters are contaminated with nasopharyngeal bacteria and are unsuitable for microbial cultivation. Endoscopy allows visualization of the respiratory tract at the time of sampling, where evaluation of the mucosa of the trachea (degree of hyperemia) and its luminal contents (quantity and quality of mucus, mucopurulent secretions, and blood) may assist in interpretation of cytologic results. Furthermore, if the length of the endoscope permits, the large bronchi may be examined, and purulent debris draining from a specific bronchus suggestive of pulmonary abscess occasionally may be recognized.

A small polyethylene catheter is passed through the biopsy channel of the endoscope and 10 to 15 ml of sterile, isotonic saline instilled. Most horses have a ventrally depressed area in the trachea, anterior to the carina and level with the thoracic inlet. Fluid accumulates at this site and forms a puddle from where it can be aspirated. The principal use of samples collected using this technique is for cytologic examination.

### Tracheal Aspirates: Endoscopic Technique Using Guarded Catheters

Recently, guarded systems have been evaluated for collection of uncontaminated samples from the lower airways via endoscopy. In adult horses, the advantages of collection using guarded catheters include noninvasiveness, speed with which samples can be obtained, visual inspection of the airways, and guidance of the catheter. These advantages generally outweigh those of the transtracheal method, which include reduced chance of bacterial or cellular contamination from the upper respiratory tract.

Several multilumen, telescoping, plugged catheters have been assessed. One is the endoscopic microbiology aspiration catheter (Catheter EMAC800, Mila International, Phoenix, Ariz.). This catheter contains a glycol plug in the outer catheter, to maintain sterility as the catheter is being advanced through the endoscope and trachea, and an inner catheter for retrieval of the sterile specimen. Another system involves a 5 French inner catheter within, an 8 French guiding catheter (Catheter V-EBAL-8.0-190, Cook Veterinary Products, Bloomington, Ind.). Before

each sample collection the endoscope and its biopsy channel must be disinfected. Glutaraldehyde (Cidex) is an appropriate disinfectant.

Some controversy remains regarding the adequacy of samples collected through guarded catheters for microbiologic cultivation. Technical prowess definitely influences the quality of sample obtained. Factors that help prevent contamination include rapid collection of the sample, limited volume of infusate (10-15 ml), and advancement of only the inner catheter into the tracheal puddle rather than the catheter as a whole. In addition, if the horse has coughed frequently during the procedure, an increased risk of contamination is likely, and these samples are rarely appropriate for bacteriologic cultivation.

## TECHNIQUE: OTHER ISSUES

### Transportation of Horses before Tracheal Aspiration

Large increases in the numbers of bacteria and inflammatory cells in the lower respiratory tract can occur within 6 to 12 hours of head confinement (e.g., cross tying, transportation). Although generally cleared within 12 hours of horses being released from confinement, clearance may be prolonged if horses are dehydrated. This has implications for collection of TAs from horses transported long distances before collection of samples. A careful history should be obtained to allow correct interpretation of results.

### Before or after Exercise

Collection of samples within 30 to 60 minutes of moderate or intense exercise may yield specimens of greater diagnostic value. These samples contain extra secretions, which more adequately represent the various regions of the respiratory tract and are more likely to reveal the presence of airway disease. However, the effect of exercise on cytologic variables of TA requires further clarification because exercise can induce inflammation in lower airways of people, and a mild neutrophilia has been demonstrated in BALs after exercise in horses. In addition, exercise may increase the degree of oropharyngeal contamination of the lower airways and thus influence results of bacterial culture. In the normal horse, this upper airway contamination is cleared rapidly by the mucociliary clearance mechanism and samples obtained approximately 30 minutes after exercise rarely contain these contaminants.

### Sample Handling

In equine practice, TA often is performed in the field, necessitating delay while samples are transported. No significant change in the relative cell counts occurs in samples stored for 24 hours at 4° C in a capped syringe. Bacterial overgrowth of samples from healthy horses does not occur, and in horses with pneumonia the numbers of aerobic bacteria does not alter over 24 hours. However, anaerobic bacteria do not survive storage and delay in processing should not occur when these bacteria are suspected.

If delays longer than 24 hours are anticipated, or access to a cool environment is not possible, a portion of the TA

should be diluted in an equal volume of a fixative solution. In these cases, the laboratory where the sample will be processed should be contacted because the method of fixation is influenced by the staining technique used. The remainder of the sample should be left undiluted for cell counts and microbiologic investigations.

## Slide Preparation and Staining

If the TA is to be processed within a practice laboratory, it should first be assessed grossly to determine the amount of mucus, mucopurulent secretions or blood present. If the TA is clear or contains only few strands of mucus, centrifugation of the sample before smear preparation is required. This may be performed using a cytocentrifuge (in which cells and other elements are transferred directly to slides during centrifugation), or samples may be processed in a routine centrifuge, the supernatant fluids decanted, and slide preparations made from the sediment.

If the sample is turbid, contains many mucus strands, or is dark red, a direct smear may be prepared from either the freshly collected sample or the fixed, diluted sample. Alternatively, dilutions of a turbid TA may be performed using sterile, isotonic saline, and the diluted sample processed by cytocentrifugation. Addition of saline to thick, tenacious samples helps dilute the cellular and mucus elements and make identification of these components easier. Smears may be stained using a variety of cytologic stains. In general, the use of a simple stain such as a modified Wright-Giemsa (Diff-Quik, Baxter, Deerfield, Ill.) is sufficient for routine analysis of TAs.

## INTERPRETATION

A number of controversial issues are associated with interpretation of TAs. Notably definitions of normal and abnormal cytologic findings, the significance of increased numbers of inflammatory cells and mucus, and the interpretation of bacteriologic results remain problematic.

### Mucus

Interpretation of the amount of mucus within a TA is best performed in conjunction with endoscopy of the lower airways. In the healthy horse, the mucociliary clearance mechanism is efficient, that is, mucus elimination keeps pace with production. Consequently, the lower airways contain little or no mucocellular material and low numbers of cells. Tracheal aspirates from normal horses are translucent gray with a few fine strands of clear mucus, and cytologic preparations contain a scant amount of mucus.

When increased amounts of mucus are observed, cytologic evaluation is essential because distinguishing between mucus and mucopurulent secretions can be difficult on gross examination. For example, a horse with a history of chronic coughing may have TA that appears mucoid and gray-white, giving the impression of septic bronchitis. However, cytology frequently demonstrates large numbers of active macrophages with copious amounts of mucus and insignificant numbers of bacteria. Thus without cytologic evaluation in these cases, inappropriate management may be initiated.

Specific causes of increased mucus include bacterial, viral, or parasitic pneumonia, chronic bronchitis, heaves, and inflammatory airway disease (IAD). In these cases, the TA contains variable amounts of thicker, more tenacious mucus, which may appear gray to cream. In cytologic preparations, the mucus may be thick and inspissated (deeply basophilic staining) or may form casts of the airways. Trapped, degenerating leukocytes may be observed within thick mucus strands. Dark coils of inspissated mucus surrounded by a translucent peripheral area (Curschmann's spirals) may be observed. However, in some cases, the significance of increased amounts of mucus in the airways remains unresolved, particularly when the neutrophils are absent or few in number. Many macrophages are activated, and no overt signs of respiratory tract disease exist.

### Total Nucleated Cell Counts

Total nucleated cell counts (TNCC) indicate the overall cellularity of a sample and assist interpretation of relative numbers of individual types of inflammatory cells. However, a number of factors influence the accuracy of TNCCs and include the variable saline dilution factor, large amounts of mucus that can trap cells, and the effect of technique. Nevertheless, both TNCC and red blood cell (RBC) counts should be performed as accurately as possible using a Neubauer hemocytometer counting chamber. Tracheal aspirates from clinically normal horses usually contain fewer than  $10^6$  cells/ml, with few to no RBCs. Samples from horses with airway inflammation have mild to moderate elevations in TNCC and may appear white, gray, yellow, or brown. Highest increases in TNCC occur in cases of bacterial pneumonia or pleuropneumonia, heaves, or lungworm infections.

### Cytology

The adequacy of the cytologic preparation first should be assessed, where a satisfactory TA contains cells from all levels of the pulmonary tree including columnar and cuboidal epithelial cells and alveolar macrophages. Limited interpretation is possible if cells from all three levels are not represented and samples should be regarded as inadequate if scant cellularity exists, or if epithelial cells predominate in the absence of macrophages.

#### Epithelial Cells

Few epithelial cells are found in TA from healthy horses, although increased numbers may be obtained when using endoscopic methods of collection. Epithelial cells are predominantly ciliated epithelial cells and may vary in size and shape. Their size reflects the site of origin, with columnar cells originating from the larger airways and cuboidal cells from the smaller airways. Squamous epithelial cells should not be present in TAs from healthy horses. However, they are observed commonly and represent oropharyngeal contamination. Identification of the presence of these cells is a prerequisite for accurate interpretation of results of microbial cultivation.

Mild changes to epithelial cells may be observed in normal horses and probably represent normal wear and tear or turnover of cells. Pathologic changes to epithelial cells

(epithelial atypia) are the result of inflammation. In cases of infectious respiratory tract disease the epithelium may be damaged directly. Although the observation of epithelial atypia may assist in diagnosis of airway inflammation, the presence of these changes is not pathognomonic for a specific etiology. In addition, claims remain unsubstantiated that increased numbers of nonciliated cells and ciliated tufts are observed in horses with poor performance and are therefore indicative of this condition.

#### Macrophages

Pulmonary alveolar macrophages (PAM) are the most abundant inflammatory cell type in TA from normal horses. Their presence, together with ciliated epithelial cells, is a prerequisite for interpretation of TA cytology because they indicate that all levels of the pulmonary tree have been sampled. Although common in normal horses, increased numbers of PAM are rare in horses with high TNCCs.

The activity of macrophages within a TA may vary considerably. Their cytoplasmic inclusions reflect the amount and type of endogenous and exogenous materials present in the lower airways. Macrophages with finely vacuolated cytoplasm are not considered abnormal, but marked increases in cytoplasmic vacuolation or large vacuoles that distort the cell and displace the nucleus are usually present only with evidence of pulmonary disease. However, care must be taken in the interpretation of ingested elements. For example, intracellular fungal spores or hyphae may be observed, but this does not mean that the horse has fungal pneumonia. In these cases other cytologic evidence of disease must be evident to confirm this diagnosis.

Low numbers of multinucleated macrophages (giant cells) are common in TAs from horses with no evidence of inflammation. Their numbers may increase with an increase in extracellular debris or chronic inflammation, but this is an inconsistent finding.

After respiratory tract hemorrhage, red blood cells within the airways are rapidly phagocytosed by pulmonary macrophages (erythrophages). The red cells are subsequently degraded, resulting in hemosiderophages. Olive green pigment indicates more recent hemorrhage, whereas older pigment becomes more golden. The amount of pigment present varies with some cells containing a few granules, whereas others contain massive deposits. EIPH is the most common cause of hemosiderophages and these cells are observed in TAs of a large proportion of horses in training. The number of hemosiderophages that is "acceptable" is controversial because the number of these cells within a TA may not reflect the total amount of blood within the airways. Much blood is likely to be cleared by mucociliary clearance and swallowed. In addition, hemosiderophages are cleared slowly and may be present months after hemorrhage has occurred. Therefore the numbers of hemosiderophages and amount of hemosiderin within the individual cells should be interpreted with caution.

The choice of performing a TA or BAL in suspected cases of EIPH also must be considered. Although samples obtained by TA contain secretions from all regions of the lungs, several studies have demonstrated that BAL may be

more sensitive for the detection of EIPH because BAL specifically can sample the caudodorsal airways.

### **Lymphocytes**

Lymphocytes are present in low numbers in normal TA and appear as small, spheric cells with scanty cytoplasm and relatively large condensed nuclei. They may be difficult to differentiate accurately from some small macrophages, stripped epithelial cell nuclei, and "end-on" epithelial cells, and this group is sometimes referred to as *small mononuclear cells*. The numbers of lymphocytes may increase in cases of respiratory tract disease, but this is inconsistent, and no correlation has been made between variations in this cell population and specific disease processes.

### **Neutrophils**

Although a population of well-preserved neutrophils reside in horse's airways, the relative percentage of these cells is thought to be normally low. However, neutrophils respond to many stimuli, and their numbers may fluctuate rapidly. In addition, neutrophils are found in higher proportions in TA than in BAL in healthy horses, and this possibly reflects the greater exposure to noxious influences in the larger more proximal airways. Furthermore, tracheal secretions are derived from many areas of the lung, and increased numbers may therefore indicate the increased probability of sampling neutrophils from somewhere in the lung.

The dilemma associated with interpretation of neutrophil percentages is to determine what value (if any) represents a significant change. Large variations in the proportion of neutrophils in healthy horses have been reported within and between studies. In addition, poor correlation between the relative numbers of cells (including neutrophils) in TA and the presence of pulmonary pathology has been observed. These observations have resulted in the usefulness of TA for assessment of chronic airway diseases to be questioned. However, studies in younger, more homogeneous populations of horses have found consistently lower values for the percentage of neutrophils in normal horses. Furthermore, recent studies in racehorses have shown low percentages of neutrophils in TA from most normal horses, a strong association between the presence of increased proportions of neutrophils and signs of respiratory disease (coughing), and an increased likelihood of isolation of significant numbers of bacteria. Other studies have shown that if other evidence of lower airway inflammation (increased mucus, increased cell count) is taken into account using an inflammation score, horses with low scores have low relative numbers of neutrophils. For these reasons less than 20% to 30% neutrophils in a TA is regarded as within normal limits in young performance horses.

The absolute numbers of cells (TNCC) present also must be taken into account when interpreting the significance of ratios of all inflammatory cells, and neutrophils in particular. For example, although neutrophils may form a relatively large proportion of cells in a sample, the actual numbers may be insignificant if the TNCC is low. The presence of toxic or degenerative changes in neutrophils may help interpretation in cases in which TNCC is low.

In the majority of cases in which the TNCC is elevated, the neutrophil is the most common type of inflammatory cell. For example, they are the predominant cell type observed in horses with bacterial pneumonia or pleuropneumonia. In these cases neutrophils are usually more than 40%, often exceeding 90%. Elevated total and relative numbers of neutrophils also may be observed in cases of IAD, EIPH, chronic bronchitis, and heaves, but the percentage is variable. Cases of interstitial pneumonia usually have low neutrophil numbers in TAs. Interpretation of increased numbers of neutrophils may be difficult in some cases but may be assisted by recognition of cytologic patterns of respiratory disease or by the use of a compound inflammation score.

The presence of toxic or degenerative changes may assist interpretation of increased percentage of neutrophils. In certain diseases (e.g., heaves, EIPH, some cases of IAD) neutrophils are mostly mature with no degenerate or toxic changes. In contrast, degenerate neutrophils commonly are observed in bacterial disease, and in these cases, careful examination of neutrophils for intracellular bacteria is often diagnostically rewarding.

### **Eosinophils**

Studies of clinically normal adult horses indicate that eosinophils are usually present in very low numbers (0% to 2%) in tracheobronchial secretions. Eosinophils may be distributed unevenly in smears, and semiquantitation may be a preferable method to expression as a percentage. Increased numbers of eosinophils in TA are most predictably observed in lung-worm (*Dictyocaulus arnfieldi*) infestations and ascarid (*Parascaris equorum*) migration. In these cases the relative percentage of eosinophils may be up to 85% of cells in the TA. Smaller elevations in the number of eosinophils in TA occur in the absence of parasitic infections and are interpreted often as evidence of a type I hypersensitivity response to inhaled allergens. However, elevated eosinophil counts in TA of horses with heaves are an inconsistent finding, although this disease has a suspected underlying allergic component.

### **Mast Cells**

Mast cells may be identified by their characteristic staining granules, which are most easily observed in preparations in which metachromatic stains are used (toluidine blue or Leishman's stain) and are stained poorly by conventional reagents (i.e., Diff-Quik). In healthy horses, mast cells are rare or present in low numbers in TAs. In samples obtained by BAL, higher numbers of mast cells may be noted. This difference may be explained by the predominant distribution of equine mast cells within the smaller airways and alveoli. Little information exists regarding abnormal percentages of mast cells in TA from horses or the significance of alterations in mast cell numbers. Studies on increased percentages of mast cells in BALs suggest they may be associated with airway hyperreactivity and respiratory embarrassment during exercise.

### **Microorganisms, Debris, and Artifacts**

A variety of microorganisms and atmospheric debris may be observed in TA from healthy horses and reflects the environment and mucociliary function at the time

of sampling. Fungal spores and occasional hyphae are the most common elements observed and may be extra- and intracellular (ingested by macrophages). Their presence does not indicate fungal infection but rather the horse's location. Pollen and plant material are common also, and other extraneous material including hairs, hay mites, and pigmented debris may be observed occasionally. Grass, dirt, and artificial racetrack surface material are common in samples collected postexercise. Bacteria rarely are observed in TA from healthy horses, but numbers are influenced by oropharyngeal contamination (squamous epithelial cells), and exercise or transportation before collection of TA. Intracellular bacteria are more likely to indicate a significant population of bacteria in the lower airways.

### Microbial Culture

Results of microbial cultivation warrant specific attention because misinterpretation of results is common. The isolation of bacteria from the TA may represent infection, a transient lower airway population or contamination of the TA at the time of sampling. Appropriate management of respiratory disease cases must differentiate between these scenarios. If bacterial respiratory tract disease is suspected, a TA should be obtained using either a guarded catheter or tracheal aspiration to confirm the diagnosis.

Aspirates from horses with bacterial lower respiratory tract infections have increased mucus, increased total cell counts, and increased relative and absolute neutrophil counts with possibly degenerative neutrophils and intracellular bacteria. Culture of a sample is not indicated without this cytologic evidence of inflammation. In addition, samples with large numbers of squamous epithelial cells should not be cultured, even if many neutrophils are present because this is evidence of contamination. If these samples are cultivated, and large numbers of bacteria are isolated, it is not possible to ascribe any significance to these isolates. Recollection of the sample is recommended.

Aerobic and anaerobic cultivation should be performed on samples with evidence of airway inflammation. Quantitative cultures, which determine the number of colony-forming units (cfu) of each species, provide additional information. Aspirates collected in an appropriate fashion from normal horses, or from horses with airway inflammation without a bacterial etiology, usually cultivate fewer than  $10^3$  bacteria cfu/ml and frequently no bacteria at all. If more than  $10^3$  cfu/ml are cultivated, it is likely that these bacteria are contributing to the disease process, and identification of species with high numbers will assist interpretation of their significance.

Identification of isolated bacteria allows differentiation of likely pathogens from likely contaminants. Bacteria commonly isolated from uncomplicated lower airway in-

fections in horses include *Streptococcus* spp. (both  $\alpha$ - and  $\beta$ -hemolytic), *Pasteurella* spp., *Actinobacillus* spp., and occasionally *Bordetella bronchiseptica* and *Mycoplasma* spp. Bacteria in the Enterobacteriaceae family (e.g., *E. coli*, *Klebsiella* spp.) are isolated more commonly after induction of antimicrobial therapy. Anaerobic bacteria (e.g., *Bacteroides* spp.) may be isolated from cases of pleuropneumonia or lung abscesses. Pneumonia in foals may be caused by all the isolates causing disease in adults, in addition to *Rhodococcus equi*. Pathogenic bacteria that rarely cause disease in the lower airways but are common contaminants of sampling include *Staphylococcus* spp. (coagulase-positive and coagulase-negative), *Pseudomonas* spp., and *Proteus* spp. Care with interpretation of these isolates must be made. Isolation of nonpathogenic bacteria indicates contamination at the time of sampling.

### SUBCLINICAL DISEASE

Subclinical respiratory tract disease is defined as an increase in mucus and numbers of inflammatory cells in the lower airways of horses with no overt evidence of respiratory dysfunction. However, the upper cutoff values considered healthy for mucus and the different inflammatory cells in TAs are currently ambiguous, which makes assessment of subclinical disease difficult. Clearly, improved definitions for normal and abnormal variables of TAs must be determined so that subtle changes can be recognized and their effects assessed. This definition may need to take into account a number of factors, such as type of housing, bedding, feed, age, and use. In addition, interpretation of the significance of subclinical disease also may vary according to the level of performance required because low levels of inflammation may have a more significant impact on horses that require optimal lung function for maximal performance.

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## CHAPTER 8.2

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# Bronchoalveolar Lavage

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**T**oday the use of fiberoptic bronchoscopy is a common and standard diagnostic procedure, which allows direct observation of the upper and lower conducting airways. During passage of the endoscope through the nasopharynx, trachea, and large bronchi, the quantity of mucous secretions can be assessed readily in addition to the degree of mucosal edema and bronchospasm. In addition to examination of the airway lumen, one of the greatest advantages and rewards from bronchoscopy is the ability to sample the large and small airways and the alveoli. The specimens collected are then analyzed for their cellular and noncellular constituents.

In recent years, bronchoalveolar lavage (BAL) using either an endoscope or specialized tubing has gained some popularity over more traditional sampling methods such as tracheal aspiration for most cases in which a diffuse inflammatory disorder is suspected. For many years, it has been assumed that sampling the lower trachea provides a representative impression of the alveoli and small airways because airway free cells from the peripheral lung eventually were swept toward the trachea for clearance.

However, a large clinical case survey of young athletic horses presented with poor performance attributable to the lower respiratory system has shown that the cytologic and bacteriologic results are correlated poorly between samples obtained from the tracheal aspirate versus those from BAL. The study demonstrated that tracheal aspirate and BAL cytologic cell differential counts differed greatly within the same horse, which suggests that samples from the tracheal puddle may not reflect accurately the population of cells and secretions present within the small airways and alveoli. This is relevant insofar as exercise intolerance, airway injury resulting from inflammation, and airway hyperreactivity are associated with disease in the small airways, reflected best by BAL cytology. In addition, a higher rate of positive bacterial cultures was obtained from tracheal aspirate samples versus BAL samples performed on the same occasion. Thus the lower trachea apparently harbors a normal bacterial flora that may not be present within the small airways and alveoli. For these reasons, BAL is becoming a more popular tool to assess distal (small) airway inflammation rather than the tracheal aspirate method of sampling.

To validate the relevance of BAL differential cell counts as a complementary diagnostic tool in the assessment of the respiratory system, other quantitative measurements are necessary beyond the routine clinical examination. In the last two decades, the syndrome of heaves has been studied extensively, and several research

laboratories throughout the world have clearly demonstrated a high correlation between the BAL cell differential and results of pulmonary function testing and histamine bronchoprovocation in heaves-affected horses. In recent years, similarly characterized lung function in young athletic horses with noninfectious inflammatory airway disease (IAD) has paralleled these findings with respect to the diagnostic usefulness of bronchoalveolar lavage.

The purpose of this chapter is to discuss the use of the bronchoalveolar lavage technique as a tool to identify and characterize pulmonary inflammation in horses that suffer from diffuse lung pathology such as IAD in the young athletic horse and the heaves syndrome in mature horses. In addition viral and bacterial pulmonary conditions are discussed briefly with respect to their diagnosis by bronchoalveolar lavage.

### INDICATIONS FOR BRONCHOALVEOLAR LAVAGE

Lower airway inflammation in horses may occur from a variety of causes. Horses of all ages can be afflicted with infectious (bacterial/viral) and noninfectious IAD and may manifest with varying clinical, physiologic and pathologic findings. In a large prospective study of 2- and 3-year-old Thoroughbred horses in training, cough and nasal discharge were second only to lameness as the most common reason for loss of training days. Noninfectious IAD is by far the most frequent respiratory abnormality encountered in both young and mature athletic horses.

The predominant feature of IAD is obstruction of the airways as a result of accumulation of secretions, thickening of the airway wall, airway remodeling, and ultimately, in advanced cases, loss of radial traction of small airways. Airway hyperreactivity is a consequence of the inflammatory process and leads to further airway closure from bronchospasm and other functional airway abnormalities. Normal horses experience bronchoconstriction in response to inhalation of aerosolized histamine at concentrations of at least 16 mg/ml. In contrast, older horses with heaves frequently develop bronchoconstriction at doses of inhaled histamine of less than 8 mg/ml. Athletic horses between the ages of 2 to 5 years with IAD develop bronchoconstriction in response to inhaled histamine at concentrations as low as 2 to 3 mg/ml, which indicates even greater airway hyperreactivity. This severe airway hyperreactivity correlates with increased presence of inflammatory cells in BAL samples, and thus BAL is an extremely

useful tool to characterize the inflammatory basis of airway abnormalities.

The incidence of poor performance attributable to the respiratory tract is significant, particularly in racing horses. Common respiratory abnormalities in this population include IAD, exercise-induced pulmonary hemorrhage, and upper airway dysfunction. In this context, IAD contributes significantly to substandard athletic performance, interruption of racing or training, and ultimately to premature retirement. In older horses (>10 years old), the prevalence of noninfectious IAD is also high, as demonstrated by a review of histologic specimens from abattoir lung samples. Therefore IAD plays a significant role in the health and performance of horses of all age groups and athletic disciplines. Bronchoscopy and bronchoalveolar lavage to elucidate the nature and degree of such inflammation is essential to understand the appropriate treatment and prognosis in each case.

Less common but also relevant to athletic horses of all ages are lung abscesses and parapneumonic effusion as septic pulmonary conditions. Such abscesses tend to be localized in the cranial portion of the right or left caudal lung lobes. Clinically these conditions can be recognized easily by the presence of an increased body temperature, inappetence, and chest pain on palpation. The suspicion of bronchopneumonia or a lung abscess is confirmed radiographically. However, performing bronchoscopy is still valuable in such patients for both diagnostic and therapeutic purposes. During bronchoscopy, reddish-brown mucoid secretions are observed readily at the tracheal puddle. With careful passage of the endoscope beyond the puddle, taking care to not disturb these secretions, it is often possible to follow the streak of discolored mucopus and to identify the specific segmental bronchus of origin. Using the biopsy channel of the bronchoscope, a polyethylene catheter can then be passed into the specific bronchus to obtain a sterile sample of the secretions for bacterial culture and cytologic analysis. Once this has been accomplished, the infusion and immediate suctioning of a low volume of fluid (~200-250 ml in two or three boluses) into the affected bronchus can be performed to remove excess exudate. This process is called *toiletage* of the airway rather than bronchoalveolar lavage. This procedure offers advantages therapeutically by reducing the bacterial challenge and exudative overload within the affected region of the lung. After the final fluid suction, a dose of antibiotic in solution can be infused locally into the affected area before retraction of the endoscope. This process can be repeated daily or on alter-nate days as a component of the treatment regime for bacterial bronchopneumonia in conjunction with systemic therapies.

### BRONCHOALVEOLAR LAVAGE PROCEDURE

BAL can be performed on most conscious horses with mild sedation (xylazine 0.3-0.5 mg/kg IV or romifidine 0.03-0.05 mg/kg IV) and airway desensitization by a local anesthetic (lidocaine solution 0.4% w/v, without epinephrine). The procedure can be conducted using either a bronchoscope 1.8 to 2 m in length or a specialized BAL

tube (Bivona Medical Technologies, Gary, Ind.). Once the bronchoscope or BAL tube is in the trachea, reaching the tracheal bifurcation (carina) usually induces coughing. Infusing 60 to 100 ml of prewarmed lidocaine solution (0.4%, without epinephrine) is therefore beneficial at this point to desensitize cough receptors located at the carina. After this infusion step the endoscope or BAL tube is gently but securely wedged, as detected by resistance to further advancement. Prewarmed sterile saline (200-300 ml) is infused rapidly into the lung and is subsequently aspirated.

The total amount of saline should be divided into two separate boluses for infusion, with attempts to retrieve as much fluid as possible between each bolus. In general, retrieval of 40% to 60% of the total amount of infusate indicates a satisfactory BAL. In horses with advanced disease, lower volumes are recovered and a tendency exists for less foam (surfactant) to be present. The BAL fluid samples are then pooled and kept on ice if processing is not possible within 1 hour after collection. Gross examination of the fluid should be performed to detect any flocculent debris or discoloration. One or two serum or ethylenediaminetetraacetic acid (EDTA) tubes of BAL fluid are centrifuged ( $1500 \times g$  for 10 min) and air-dried smears are made from the sample pellet after removal of the supernatant. In preparation of the smears, the slides must be air dried rapidly using a small benchtop fan to preserve good cellular morphology. Smears thus prepared can be kept at room temperature for up to 8 to 10 months with little cellular alterations. The air-dried smears can be stained with Diff-Quik, Wright-Giemsa, May Grunewald, Leishman's, or Gram's stain for cellular and noncellular constituent interpretation. The cellular profile and morphology may serve as a guide to the nature of airway injury, inflammation, and the pulmonary immunologic response to infections or foreign antigens.

### DIFFERENTIAL CELL COUNTS AND THEIR INTERPRETATION

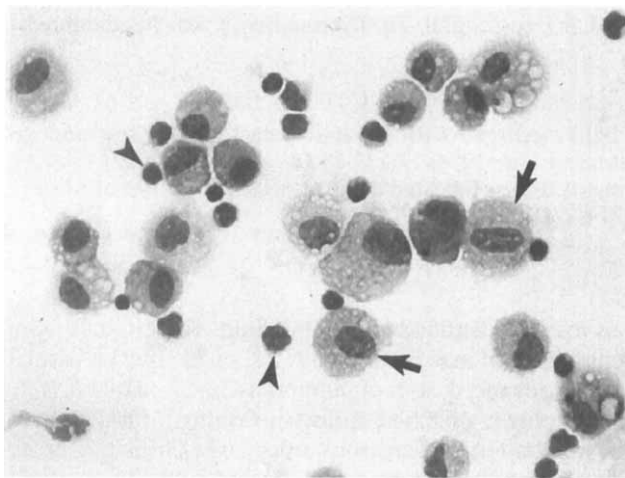
Under field conditions, the amount of infused fluid often varies, ranging from 60 ml to 300 ml of sterile saline per BAL. In addition the volume of fluid retrieved may be reduced dramatically in horses with severe bronchospasm. For these reasons, dilutional effects compromise the accuracy of total nucleated cell counts. Therefore the total cell count offers little clinical importance to the interpretation of inflammatory lung conditions because the reference range for total nucleated cell counts is very broad and deemed meaningless.

On the other hand, the differential count of cell types is largely unaffected by dilutional variance and is useful to characterize abnormal increases in specific cell populations. The differential cell count is therefore able to identify distinctive features of septic, nonseptic, and viral inflammatory airway conditions and is useful to guide decisions in the therapeutic approach of each individual case. Reference ranges for BAL differential cell counts have been developed for normal horses, horses with heaves, and poorly performing athletic horses. Characteristic cytologic features are evident in each respective group.



### Differential Cell Counts in Healthy Horses

Reference ranges for BAL differential cell counts have been derived from BAL sampling in horses free from respiratory disease, as characterized by a variety of methods including clinical examination, pulmonary function testing, and in some cases by lack of airway hyperresponsiveness to bronchoprovocation with aerosolized histamine (Figure 8.2-1). In young horses (<6 years of age), the distribution of macrophages, lymphocytes, neutrophils, mast cells, and eosinophils in the BAL fluid is on average 65%, 30%, 3%, 0.5% and 0%, respectively (Table 8.2-1). However, in mature horses (>6 years of age), the neutrophil population may average up to 15% in healthy horses as defined by the above diagnostic methods, with a corresponding decrease in the percentage of macrophage and lymphocyte populations.



**Figure 8.2-1** Normal bronchoalveolar lavage cytology (500 $\times$ ) from a young athletic horse demonstrating macrophages (arrows) and lymphocytes (arrowheads). (Courtesy Laurent Viel and Joanne Hewson, Guelph, Ontario, Canada.)

### Abnormal Differential Cell Counts

#### Young, Athletic Horses

In young athletic horses with poor performance and clinical signs referable to the lower respiratory tract such as coughing, poor recovery from exercise, or decline in performance, the BAL cell differential shows a broad spectrum of inflammatory cell profiles. A single type of inflammatory cell, such as the mast cell, eosinophil, lymphocyte, or neutrophil may predominate in the BAL fluid, or a mixed inflammatory response may be observed. As the BAL sampling technique becomes more widely used by veterinarians, it has become evident that a large percentage of athletic horses have some degree of airway inflammation, with a wide range of severity. Predominance of a single cell type apparently occurs early in the course of pulmonary inflammation. A mixed population of inflammatory cells is observed more frequently as the inflammatory response progresses.

Distinct BAL cytologic profiles that have been recognized in athletic horses are highlighted in Table 8.2-2. In terms of classification of the underlying immunologic response, an increased population of mast cells in the airway suggests the presence of type-I hypersensitivity. In contrast, elevated numbers of neutrophils are felt to reflect an allergic type-III hypersensitivity reaction. Caution should be exercised when using these terms, however, because immune complex deposition in the pulmonary vascular bed or airway submucosa during true type-III hypersensitivity has not yet been demonstrated in the horse to date.

An elevated population of eosinophils in BAL fluid of horses is generally a transient finding, and such an increase is seldom repeatable despite performing a second BAL within 24 hours of the first sample collection. BAL eosinophilia is most often encountered in conjunction with an increased population of mast cells and is considered to reflect recruitment of eosinophils in response to increased mast cell degranulation. Thus BAL eosinophilia is particularly evident when the majority of mast cells in the sample have degranulated, demonstrated by the appearance of a basophilic granular background on the

**Table 8.2-1**  
**Bronchoalveolar Lavage Cytology of Normal Young and Older Horses (Mean  $\pm$  SD)**

n	Breed	Age	Mac (%)	Lymph (%)	PMN (%)	MC (%)	EO (%)	Author†
6	Stb	2.7 $\pm$ 1.1	64 $\pm$ 5	28 $\pm$ 3	4 $\pm$ 0.3	0.3 $\pm$ 0.3	1 $\pm$ 1	Moore 1995
12	Stb	3.1 $\pm$ 0.9	60 $\pm$ 5	37 $\pm$ 5	2 $\pm$ 1	0.4 $\pm$ 0.4	0.03 $\pm$ 0.1	Hare 1994
11	TB	3.2 $\pm$ 1.2	65 $\pm$ 6	28 $\pm$ 6	7 $\pm$ 3	0.2 $\pm$ 0.7	0	Fogarty 1991
6	Stb	3.5 $\pm$ 1	68*	32*	0.4*	1*	0.3*	Hare 1998
6	Stb/TB	13.5 $\pm$ 3.6	34 $\pm$ 4	45 $\pm$ 4	14 $\pm$ 5	0.9 $\pm$ 0.3	2.3 $\pm$ 1.6	Tesarowski 1991

Mac, Macrophage; Lymph, lymphocyte; PMN, neutrophil; MC, mast cell; EO, eosinophil; TB, Thoroughbred; Stb, Standardbred; SD, standard deviation.

\*Data expressed as median value.

†All studies are in chapter readings list except the following:

Hare JE, Viel L, O'Byrne PM et al: Effect of sodium cromoglycate on light racehorses with elevated metachromatic cell numbers on bronchoalveolar lavage and reduced exercise tolerance. *J Vet Pharmacol Ther* 1994; 17:237-244.

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Table 8.2-2

**Bronchoalveolar Lavage Cytology of Young and Mature Horses with Signs of Respiratory Disease (Mean  $\pm$  SD)**

n	Breed	Signs	Age	Mac (%)	Lymph (%)	PMN (%)	MC (%)	EO (%)	Author†
5	Stb	Poor performance or cough	2.6 $\pm$ 0.9	59*	26*	0.8*	1.4*	12*	Hare 1998
12	Stb/TB	Poor performance	3.4 $\pm$ 1.6	57 $\pm$ 12	36 $\pm$ 14	4 $\pm$ 3	4 $\pm$ 2	0.5 $\pm$ 0.3	Hare 1994
15	Stb	Poor performance	3.7 $\pm$ 0.3	48 $\pm$ 2	36 $\pm$ 2	10 $\pm$ 1	2 $\pm$ 1	4 $\pm$ 1	Moore 1995
65	TB	Poor performance	4.3 $\pm$ 1.9	64 $\pm$ 15	23 $\pm$ 11	13 $\pm$ 12	0.3 $\pm$ 0.7	0.1 $\pm$ 0.3	Fogarty 1991
20	Stb	Poor performance or cough	8 $\pm$ 0.3	46 $\pm$ 1	49 $\pm$ 2	3 $\pm$ 0.3	3 $\pm$ 0.4	0.2 $\pm$ 0.05	Hoffman 1998
6	Stb/TB	Heaves	10 $\pm$ 1.7	30 $\pm$ 6	33 $\pm$ 4	35 $\pm$ 10	0.9 $\pm$ 0.3	0.7 $\pm$ 0.2	Tesarowski 1996

Mac, Macrophage; Lymph, lymphocyte; PMN, neutrophil; MC, mast cell; EO, eosinophil; TB, Thoroughbred; Stb, Standardbred; SD, standard deviation.

\*Data expressed as median value.

†All studies are in chapter readings list except the following:

Hare JE, Viel L, O'Byrne PM et al: Effect of sodium cromoglycate on light racehorses with elevated metachromatic cell numbers on bronchoalveolar lavage and reduced exercise tolerance. *J Vet Pharmacol Ther* 1994; 17:237-244.

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cytologic smears and granules phagocytized by alveolar macrophages. Such animals are frequently hyperreactive to passage of the endoscope and display paroxysmal coughing and apparent bronchospasm induced by wedging of the endoscope for the BAL procedure.

Occasionally, a predominance of eosinophils may be observed in the BAL fluid without a concurrent increase in mast cell numbers. Lung biopsy taken from such horses demonstrates granuloma-type clusters of eosinophils in the peribronchiolar area and alveolar interstitium. In these cases, the BAL eosinophilia reflects true idiopathic pulmonary eosinophilia rather than increased recruitment to the lung. The etiology of this type of pulmonary eosinophilia is unknown and has not been correlated with lung parasitism because it has been observed in horses with a recent and routine deworming history.

Another cellular constituent frequently observed in the BAL fluid of young athletic horses is the globule leukocyte. Although these cells are similar in morphologic appearance to mast cells on light microscopy, the globule leukocyte has cytoplasmic granules approximately 10 times larger than mast cell granules. The granules of globule leukocytes assume a grapelike cluster appearance when separated from the mother cell. Caution should be taken to not confuse the globule leukocyte with intact, exfoliated goblet cells. The function of these metachromatic cells and their released mediators in horses is still unclear. From a clinical perspective, however, horses with a large percentage of globule leukocytes on the BAL differential count tend to have a much poorer response to treatment with mast cell stabilizers or corticosteroids.

As airway inflammation progresses, Curschmann's spi-

als may be identified in the BAL fluid. These spirals represent a mucoid matrix that plugs the small airways, particularly in advanced cases of pulmonary inflammation. As the mucus plug is stretched during suctioning for BAL fluid retrieval, the long filamentous airway cast ultimately breaks and forms a characteristic spiral during recoil. The presence of Curschmann's spirals reflects a state of chronic airway remodeling and thus bears a more guarded prognosis. In athletic horses with chronic inflammation evidenced by the presence of mixed cellular populations and Curschmann's spirals, a high rate of relapse is observed despite several weeks of antiinflammatory treatment or when low-dose maintenance treatment is administered.

Although epithelial cells are not considered to be inflammatory cells for purposes of the differential cell count, the number of single cells or epithelial clusters observed on BAL cytologic preparations should be noted. The presence of exfoliated epithelial cells may result from either mucosal injury resulting from trauma during the BAL procedure or may reflect true cellular damage caused by an acute or chronic inflammatory process. The latter may occur with infectious causes such as viruses, or may occur through noninfectious inflammatory-mediated airway mucosal injury, such as severe exacerbation of airway inflammation (heaves).

In recent years, BAL has been used by researchers to quantify the severity of exercise-induced pulmonary hemorrhage (EIPH) in racing horses based on the percentage of hemosiderin granule-laden macrophages present in BAL fluid. Although this technique has application in studying EIPH experimentally, perhaps more relevant from a clinical perspective is the concomitant presence of airway inflammation recorded in these horses with EIPH. Bron-

choalveolar lavage cytology in the majority of EIPH-affected horses shows a mixed inflammatory cell population of principally neutrophils, mast cells, and eosinophils. Thus the prognosis for horses identified with this mixed airway inflammation tends to be guarded due to the concurrent presence of EIPH and IAD.

Interpretation of BAL cytology in young athletic horses with exercise intolerance is incomplete without a discussion of the characteristic cytologic findings that accompany respiratory viral infections. Extensive columnar ciliated epithelial cell exfoliation was detectable in BAL specimens of horses after experimental infection with either influenza or herpes viruses. The cytologic smears featured numerous detached ciliated plates, and free cilia also were visible in the smear background. These characteristic cytologic findings seen with viral respiratory infection frequently are recognized under racetrack conditions, particularly in early fall and mid-winter according to the seasonal pattern of viral respiratory disease transmission.

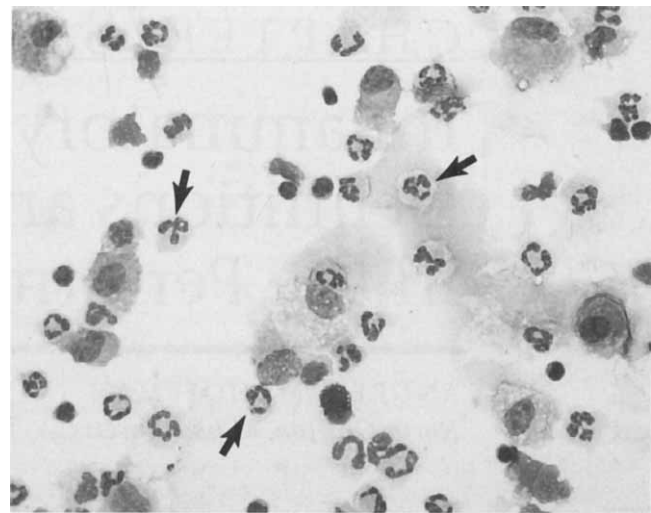
### **Mature Horses**

In contrast to young athletic horses, mature horses generally do not express overt clinical signs of respiratory disease, particularly when affected by a respiratory viral infection. If the disease is endemic in a stable, mature horses generally display only mild signs or remain subclinical and frequently recover within 5 to 6 days without therapeutic intervention. However, a few horses may present with what appears to be a persistent and ongoing respiratory viral infection. In these cases, the viral infection often has resolved but seems to have exacerbated a persistent inflammatory airway response, which is characterized in the BAL cell differential by a significant increase in mast cells and/or neutrophils.

The heaves syndrome is a commonly diagnosed respiratory condition in mature horses with a definitive typical history, clinical appearance, pulmonary function test abnormalities, and airway hyperreactivity. By definition, horses with heaves exacerbation have at least 25% neutrophils in their BAL (Figure 8.2-2). However, neutrophils frequently account for more than one third of the total inflammatory cell differential in such cases and play a pivotal role in the clinical syndrome and pronounced airway hyperreactivity. The BAL cytologic smear in heaves-affected horses frequently displays a heavy mucoid background, with many nontoxic and apoptotic (senescent) neutrophils entrapped within this mucus. The BAL of heaves-affected horses also shows a significant increase in the overall number of mast cells, eosinophils, lymphocytes, macrophages, and epithelial cells in addition to the increased neutrophils. These cells must be recognized and assessed apart from the neutrophils. The number of exfoliated epithelial cells tends to be elevated as a result of mucosal injury caused by the severe inflammatory process. In addition to cellular constituents described above, BAL smears in heaves-affected horses often show noncellular structures such as Curschmann's spirals reflecting chronic nonseptic inflammatory airway disease.

### **CONCLUSION**

BAL is undoubtedly becoming a powerful ancillary diagnostic tool to assist in the diagnosis of clinical and subclinical lower airway respiratory conditions such as non-



**Figure 8.2-2** Bronchoalveolar lavage cytology (500 $\times$ ) showing a significant percentage of neutrophils (arrows) in the differential cell count. (Courtesy Laurent Viel and Joanne Hewson, Guelph, Ontario, Canada.)

infectious inflammatory airway disease in the young athletic horse and recurrent airway obstruction, or heaves, in older horses. Using recognized, standardized procedures, the BAL differential cell count is fairly consistent for normal horses and any alteration in the cytologic profiles from normal values identifies a wide range of nonseptic inflammatory processes. Although at present, clinicians are recommending specific treatment according to cytologic findings of the BAL cell differential, a more in-depth knowledge of the various disorders in the future may allow equine practitioners to provide more accurate prognostic information to members of the horse industry with respect to respiratory diseases in athletic horses. More so, the majority of young and mature athletic horses with an excess amount of white mucopus within the airways and markedly elevated neutrophil percentage on the cell differential do not represent a septic process. Rather, these cases demonstrate nonseptic inflammatory airway disease.

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## CHAPTER 8.3

# Inflammatory Airway Diseases: Definitions and Diagnosis in the Performance Horse

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For many years, veterinarians have recognized that lower respiratory disease can compromise performance in horses. However, until recently lower airway diseases, excluding heaves, have received little scientific attention. Many horses have no history recognizable as heaves, and, on examination, fewer than 50% of horses with chronic cough and excessive secretions have abnormal breathing patterns or auscultation findings or elevated intrapleural pressure changes. Clearly, many horses with lower airway disease cannot be diagnosed with heaves.

The earlier, milder form of lower airway disease is often quiescent, stems from low-grade inflammation rather than heaves, and presents with waves of severe inflammation and labored breathing. This subclinical aspect of lower airway disease is why the mysteries of this problem have remained unsolved for so long. Examples of puzzling questions include the following:

- Does a horse that coughs more than four times at the beginning of exercise and has mucus on endoscopy have lower airway disease?
- If mucus is obtained and bacteria are cultured, is an infection present?
- What is the standard for cytologic diagnosis?
- If a horse responds to corticosteroid treatment by running faster, did it have “allergic airway disease?”

Equally puzzling is the functional significance of the clinical signs such as cough and mucus in the trachea. The signs can be elusive and misleading because no definitive algorithm exists. Controversy about lower airway disease continues because of the lack of standard diagnosis and treatment. For instance, a cough and mucus in the airways may signify local tracheobronchial irritation or global small airway (bronchiolar) inflammation. The former is a transient nuisance perhaps requiring no action other than rest; the latter may affect performance and portend long-term consequences.

Thus one pivotal aspect of the decision-making process of veterinarians is to sort out the functional significance of clinical observations. Recent advances in pulmonary function testing have made this possible. Furthermore, the treatment and prevention methods for heaves do not address the unique training environment of the younger horse. For example, less than 50% of horses with a history of chronic cough respond to initial environmental man-

agement. Therefore management for the young horse must be tailored specifically to this problem, and a number of suggestions are provided in other chapters (Chapter 8.4: “Heaves (Recurrent Airway Obstruction): Practical Management of Acute Episodes and Prevention of Exacerbations” and Chapter 8.10: “Use of Aerosolized Bronchodilators and Corticosteroids”).

## DEFINITION

The terms *chronic obstructive pulmonary disease (COPD)* and *chronic bronchitis* were used for many years to describe a spectrum of lower airway inflammatory diseases. Currently a strong consensus exists that the term *COPD* should be retired. Comparative physiologists and scientists who wish to make progress in the research of lower airway diseases in horses want to distinguish the equine from the human condition. *COPD* describes a syndrome in humans that is distinct from that in horses, that is, a fixed (less reversible) and less episodic lower airway obstruction primarily caused by smoking.

In 2001 an international panel of veterinarians who investigate equine airway disease suggested that lower airway diseases be divided into two major entities. The first, *heaves* (synonymous with recurrent airway obstruction, or *RAO*), describes horses with episodes of obstructive lower airway disease, triggered by exposure to moldy hay, characterized by expiratory dyspnea, and found with severe airway inflammation with a large percentage (>25%) of neutrophils, airway hyperreactivity, and reversibility with bronchodilator treatment. The second is inflammatory airway disease (*IAD*), which includes infectious or noninfectious problems of the lower airways (e.g., bronchitis and bronchiolitis), apart from heaves, and separate from infections of the lung parenchyma (pneumonia) or pleura (pleuropneumonia). The clinical signs of *IAD* typically are not precipitated by exposure to moldy hay, although inflammation is noted with prolonged exposure to moldy hay or exposure to endotoxin by inhalation in some horses with *IAD*.

## CLINICAL SIGNS

Inflammatory airway disease is used to describe the signs of cough, exercise intolerance, and mucus accu-

mulation in the airways. The discipline of the horse determines the exact signs. In racehorses, fading at the  $\frac{1}{2}$ - or  $\frac{3}{4}$ -mile mark is a typical complaint. Coughing can be a prominent sign, especially with a lack of response to antimicrobials.

Often poor performance is perceived at a time when the problem is not diagnosed easily by clinical or endoscopic examination. The trainer may observe abnormal behaviors that indicate hesitation or reduced stamina at work. Obscure as they are, these observations have been associated with lower airway inflammation and lung dysfunction and must be considered as indicators of airway disease until proven otherwise. Other signs include poor exercise recovery, or overheating. In sport horses, usually more advanced in age, common clinical signs are coughing in the stable or at the beginning of exercise, with progressive refusal of work. The cough is usually mild but may become spasmodic, and the rider may be jolted in extreme cases. The cough may be shallow or deep, but usually signs of mucus production are present, such as subsequent jaw movement or swallowing. The level of preoccupation with coughing varies considerably but clearly interferes with work. Dressage horses may be reluctant to collect and have difficulty with flexion of the head and neck. These horses show progressive lethargy and loss of impulsion, and they eventually stop. Lung dysfunction, despite the lack of visible heaves, becomes pronounced and disruptive.

Mucus in the airways is an inconsistent finding that cannot be used to define IAD. However, endoscopically visible mucus customarily is believed indicative of IAD. Many horses with mucus do not cough, although most coughing horses have mucus in their trachea. Successful prediction whether a horse with cough or mucus has lung dysfunction is impossible, although chronic cough is a strong indicator in this author's experience. In some cases, fine white mucus can be observed at the nares, particularly after exercise.

Many horse owners ignore these signs initially, and they assume some coughing is normal. Coughing is not normal if it is associated consistently with the onset of exercise, occurs spontaneously in the stable or during feeding, is deep and productive, or reduces performance for any reason. Some coughing in response to arena dust may not indicate lower airway disease, but the distinction cannot be made on the basis of the cough sound or auscultation of the lungs.

## INFLAMMATION OF THE LOWER AIRWAYS

Evidence indicates that lower airway inflammation is prevalent in the horse. This relates to stable, arena, and paddock conditions that put the horse at risk, in addition to constant challenges with viruses and bacteria. Exercise may increase lower airway inflammation, but evidence for this is scant in the equine species. Little information exists regarding the nature of inflammation in IAD. By association, studies in horses with heaves have demonstrated the presence of allergic phenomena (increased cytokines IL-4, IL-5 and reduced interferon gamma, increased mast cells and neutrophils, reduced antiproteases, increased procoagulants, histamine, leukotrienes, metalloproteinases, and

other inflammatory mediators). In early studies many horses with "COPD" (pre-heaves) had increased viral (influenza) antigen in their tracheal mucus. Furthermore, influenza infection caused prolonged inflammation and airway hyperreactivity similar to the inflammation observed in some horses with IAD.

Other studies have shown that exercise-induced pulmonary hemorrhage causes transient neutrophilic inflammation. Thus far, two studies have shown a lack of association between EIPH, airway inflammation, and lung dysfunction. Evidence exists of a genetic basis for heaves in families of horses, but the basis for this tendency has not been discovered. Some researchers also have found mechanical dysfunction in horses with IAD that might suggest a congenital tendency towards bronchoconstriction, but the structural basis for this finding is unknown. Endotoxin derived from stable manure also has been implicated as a cause of inflammation in the airways. In conclusion, the pathogenetic basis of the inflammation is unknown, but it is surely multifactorial.

Inflammation can be characterized using transtracheal aspiration (TTA) or bronchoalveolar lavage (BAL; see Chapters 8.1: "Tracheal Aspirates: Indications, Technique, and Interpretation" and Chapter 8.2: "Bronchoalveolar Lavage" for a description of the techniques). The TTA samples the central airways (a collection of all secretions) and the BAL a more peripheral segment of lung. Large surveys of poor performance racehorses using BAL cytology have revealed abnormalities in cytology such as increased neutrophils, mast cells, lymphocytes, or eosinophils, that distinguish the horses with IAD from controls. Despite the large numbers of inflammatory cells in BAL, these samples reveal no evidence of infection. In later studies, BAL inflammation was associated with pulmonary dysfunction in both racehorses and non-racehorses. Multiple studies in sport horses with exercise intolerance found that an increase in BAL mast cells or neutrophils is associated with abnormal lung function, that is, small airway obstruction, expiratory flow limitation, and/or airway hyperreactivity (i.e., the tendency to bronchoconstrict). In particular, horses with exercise limitations and airway hyperreactivity, in comparison with control horses, had an elevation of mast cells and leukotrienes. These studies confirm that some horses with IAD have a marked functional disturbance that limits performance. The mast cell may play a pivotal role in releasing inflammatory mediators that cause bronchoconstriction and mucus production and act as growth factors to increase airway wall thickening. Although the evidence is strong that this is an allergic type phenomenon, insufficient proof exists to substantiate the use of the phrase "allergic airway disease."

In exercise studies using metabolic stress tests on the treadmill to determine aerobic capacity ( $\dot{V}O_{2\max}$ ), poor performance often is related to lower airway disease, detected by neutrophilic inflammation on TTA in many cases. From these large studies, researchers concluded that bronchitis or bronchiolitis play a significant role in exercise intolerance, although no direct statistical link is made between the degree of inflammation and  $\dot{V}O_{2\max}$ . Further studies are warranted to understand the link between inflammation and reduced exercise tolerance.

## INFECTION AS A RISK FACTOR FOR INFLAMMATORY AIRWAY DISEASE

The role of infection in IAD should not be ignored. Viral infections are highly prevalent. Studies show that viral illness causes major economic losses in the equine industry, but the association between viral illness and IAD is speculative at this time. Viral infections can cause inflammation and functional disturbances including upper and lower airway obstruction, bronchoconstriction, and airway hyperreactivity. However, viruses rarely are recovered from TTA specimens in horses that are coughing chronically.

Field investigations using TTA as a standard for IAD provide insight into the role of bacteria in respiratory disease of racehorses. In coughing racehorses, mucus usually is found on endoscopy, and TTA samples reveal a neutrophilic cytology and the presence of bacteria. Mucus and inflammation also can be found in many horses that do not cough. However, bacterial numbers are greater in coughers than noncoughers, so bacterial colonization or infection is a risk factor for coughing. If IAD is defined as coughing, mucus, and TTA neutrophilia, about 50% of these horses have evidence of infection. The other 50% presumably have a primary noninfectious basis for coughing and mucus or the latter are a sequel to prior infection.

Is it possible to reconcile the results of studies of IAD based in the field, where infection is much more commonly diagnosed, from studies based in referral hospitals where bacteria are less commonly implicated? Antibiotics administered to the horse at the racetrack may eliminate visible bacteria from the cytologic preparations made at the time of examination in the referral hospital. Also, many cases of cough, tracheobronchial mucus, and presence of bacteria often are dealt with successfully in the field; only those horses that subsequently fail to perform adequately are referred for further work-up. Furthermore, the etiology of the acute early cough may differ from that of the chronic condition present at the time of examination. In horses with loss of performance, the problem is usually chronic, which may present a shift in pathophysiology. These horses have structural changes in their airways, not simply irritation and infection, and these structural changes take time to develop.

Another inconsistency in the approach to IAD has to do with the definition of *infection*. In the studies of coughing in Thoroughbred racehorses, multiple species of bacteria were recovered by TTA, some considered typical bacterial pathogens (*Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Actinobacillus lignieresii*) and others not. Previous studies of normal stabled racehorses also have found a high prevalence of bacteria in the trachea.

Therefore the interpretation of tracheally derived bacteria in racehorses must be made cautiously. The assumption, for instance, that 1000 colony-forming units per gram of tracheal secretions means infection is presumptive. This bacterial load (or lesser quantities) also may be interpreted as opportunistic colonization without infection. Furthermore, many (50%) of the horses in these epidemiologic studies had no infectious agent recovered, which supports the notion that many of the bacterial infections were secondary to another noninfectious process.

Racehorses frequently aspirate foreign material, including dirt and pollutants, as evidenced by squamous

cells in TTA samples, for example. Bacterial colonization and laboratory studies have shown that air pollution promotes bacterial growth in the respiratory tract of animals. So what is "infection," and what is its role in causing inflammation in racehorses? This warrants further study.

In non-racehorses, infections are uncommon. In these horses with cough, neutrophils and fibrillar mucus without bacteria is common. Therefore distinguishing between race and non-racehorses is important in interpretation of the type of inflammation and signs.

## FUNCTIONAL DISTURBANCES ASSOCIATED WITH INFLAMMATORY AIRWAY DISEASE

Horses can have significant lung dysfunction including lower airway obstruction without any visible signs such as abdominal lift, nostril flaring, abnormal lung borders on percussion, or abnormal lung auscultation. In one survey, fewer than 50% of horses presenting with chronic cough or exercise intolerance had increased pleural pressure changes. In this author's experience, detection of abnormal lung sounds, despite the vigorous use of the re-breathing technique, is rare in horses other than those with a history of heaves. The non-heaves horse with exercise intolerance, similar to the horse with outright heaves, however, has remarkable lung dysfunction. The analogy is the human with asthma who contends with episodes of bronchoconstriction on a daily basis without any outward signs, other than reaching for an inhaler. In the horse, the virtual lack of clinical signs despite lower airway obstruction can be explained in physiologic terms:

1. The horse has tremendous reserve capacity and may be hypoxemic only when challenged with exercise
2. The small airways contribute minimally to the total respiratory system resistance (>30%), and therefore abnormalities in resistance of the respiratory system are affected minimally by small airway disease until it is severe, or at a time when clinical signs are obvious. In sum, it is a misconception that only horses with heaves have significant lower airway obstruction that can be measured readily with pulmonary function tests.

The primary functional disturbance in horses with IAD with exercise intolerance and/or cough is airway obstruction. Studies have demonstrated that airway obstruction involves principally the small airways (bronchioles), presumably compromising gas exchange during exercise via uneven distribution of ventilation. Histologic studies support epithelial hyperplasia in bronchioles as an important change that reduces the airway lumen diameter. Goblet cell metaplasia and smooth muscle hypertrophy are not particularly pronounced in horses with IAD that exhibit functional disturbances, but they are important in horses with heaves. Overall, cough is a result of airway inflammation that causes irritation and stimulates mucus accumulation, bronchoconstriction, and airway hyperreactivity. Therefore the pathophysiology of cough and exercise intolerance are linked inextricably.

Does a link exist between IAD and heaves? Yes, in this author's opinion. Horses advancing in age (>10 years) are at risk for a functionally significant form of IAD, which closely resembles heaves with respect to the nature of lung

dysfunction. Perhaps equally compelling, however, is the evidence presented in the medical backgrounds of horses with heaves. Many owners of horses with heaves describe at length, and sometime provide diaries as evidence, that their horse had respiratory signs, including cough, mucus, exercise intolerance, for several years before the first episode of heaves. If it were not for the relief of the seasons and various attempts at environmental management throughout the years, it seems likely that heaves would develop faster in many of these horses.

### **PULMONARY FUNCTION TESTS: DIAGNOSIS OF FUNCTIONAL DISTURBANCES ASSOCIATED WITH INFLAMMATORY AIRWAY DISEASE**

Recently three major advances have been made in testing the functional significance of lower airway diseases in the horse, which have somewhat supplanted the conventional method of lung function testing. The conventional, time-honored system of testing lung function using an esophageal balloon catheter (passed like a stomach tube) and pneumotachograph is invasive and requires significant expertise. Nevertheless, for horses with significant lung dysfunction, an accurate measurement of airway obstruction is obtained by this method. Of three newer methods, two methods, oscillometry and forced maneuvers, are employed in referral hospitals and the third, flowmetrics, is adapted for use in the field.

Oscillometry (forced oscillatory mechanics) is a technique for measuring lung function in greater detail and allows the discrimination of large (bronchi) versus small (bronchiole) airway obstruction. Only a facemask is required as an interface. A baseline measurement of respiratory system resistance and other variables is taken over a series of driving frequencies, using compressed room air as the input signal. Because the system ignores natural breathing frequencies it is possible to analyze the effects of the externally forced oscillations on the respiratory system. After a baseline is obtained, the horse is exposed to histamine by aerosol to determine airway reactivity. Airway reactivity is measured as the dose of histamine that induces a known degree of airway obstruction. Horses with IAD exhibit increased respiratory system resistance (obstruction) at baseline, particularly involving the small airways, a unique pattern of constriction, which is more evident at the lowest frequencies of testing ("frequency dependence"), and airway hyperreactivity. These are important functional disturbances that relate to poor performance. The effects of treatment on these lung function variables can be monitored after 30 and 60 days of treatment. Often, the functional disturbances, in particular, the abnormal pattern of constriction reverses, although in some cases airway hyperreactivity and a degree of airway constriction persist. This program allows the clinician to decide on the duration and intensity of treatments and the need for long-term maintenance treatment and reevaluations of lung function.

Another method used to confirm the presence of a functional disturbance in horses with signs of IAD is forced expiratory maneuvers. This system is most similar to that used in human medicine. In this method the horse

is forced to exhale as hard as possible, starting from total lung capacity, using a nasotracheal tube and a special suction device. Expiratory flow limitation can be observed early in the course of disease. Histamine challenge studies also can be performed with this method.

A new field method (flowmetrics) recently was developed, which allows airway reactivity to be measured in the field. The baseline measurement (before histamine) is taken, followed by histamine challenge. The baseline measurement is less sensitive than the other systems, but the results of the histamine challenge are just as accurate as conventional or oscillometric methods. Most, if not all, horses with IAD and exercise intolerance have airway hyperreactivity; therefore the flowmetric system can be used to measure airway reactivity in the field and rule out this potential disturbance in horses. Results from the flowmetric device were shown to be highly repeatable.

These methods have been used in horses and have excellent documentation in the literature. In the future, the use of pulmonary function tests in the field or as a referral will be common, primarily because of the high prevalence of IAD as a cause of poor performance.

### **DIAGNOSTIC APPROACH TO RACEHORSES WITH COUGH BUT NO LOSS OF PERFORMANCE**

The diagnosis of IAD is made on the basis of coughing and the presence of excess or thickened (mucopurulent) mucus observed endoscopically. The appropriate action is to sample tracheal secretions, preferably after exercise, using a sterile method (plugged catheter through an endoscope or percutaneous TTA) and to have the secretions examined by a cytopathologist familiar with equine respiratory cytology. Secretions also should be cultured and sensitivities sought. The presence of excessive neutrophils with a degenerative appearance and/or intracellular bacteria is sufficient for a diagnosis of sepsis, and appropriate antimicrobials should be instituted for a minimum of 5 days. The choice of antibiotics, length of treatment, and dosage depend entirely on regional susceptibilities and preferences. The presence of hematologic abnormalities also should prompt further investigation of the lung, including radiographs and/or ultrasound.

If a lack of response to antimicrobial treatment occurs, the TTA and the ancillary imaging tests should be repeated. The absence of sepsis may lead to suspicion of either poor mucociliary clearance or excess mucus production. In the horse without performance issues the horse may benefit from increasing turnout, reducing stress, and promoting rest. Some horses respond to a change in diet away from hay. If coughing continues despite adequate treatment, further diagnostics, such as bronchoscopy, may be helpful. Occasionally, chronic cough may be due to a foreign body.

### **DIAGNOSTIC APPROACH TO RACEHORSES WITH A DECLINE IN PERFORMANCE**

In these horses, the main concern is poor performance and a functional disturbance should be considered. Cough or endoscopic evidence of mucus may be present. The veterinary professional must decide whether infection underlies

poor performance or whether a nonseptic condition is present. Therefore it is advisable to collect a TTA for cytologic evaluation if signs of infection exist (e.g., fever, hematologic abnormalities, outbreak conditions) and abnormal mucus is in the airways, or if the horse is coughing.

The absence of signs of infection should lead to consideration of bronchoalveolar lavage (BAL) cytology and/or pulmonary function tests. The practitioner is more likely to discover the cause of poor performance using a BAL than TTA. The cytology and culture results from TTA do not represent that of the BAL (see Chapter 8.2: "Bronchoalveolar Lavage"). Inflammation on BAL correlates with airway obstruction, airway hyperreactivity, and greater hypoxemia with intense exercise, not with TTA inflammation. Therefore apparently the functional disturbance that causes poor performance involves the small airways in the lung periphery, and sensitive tests to diagnose this problem are required.

The TTA is not sensitive and specific enough to make this distinction. Many horses harbor inflammation (IAD) without performance problems, and a wide range of normal neutrophil counts in TTA (0%-20%) exists. In contrast, abnormalities on BAL are indicative of a functional disturbance (uneven ventilation, bronchoconstriction) that necessitates specific treatment. The normal range for neutrophils in BAL is narrow (0%-5%), which allows for greater precision in diagnosis. A TTA or BAL also can be used to confirm EIPH if it was not observed endoscopically before this investigation.

### DIAGNOSIS OF INFLAMMATORY AIRWAY DISEASE IN NON-RACEHORSES WITH COUGH

Not all coughs are caused by IAD in sport horses, although infection is considerably less common than in racehorses. Coughing is a normal clearance mechanism and, in many horses, coughs can arise (without IAD) from exposure to dust in an arena (mold, particles from arena floors) or paddock (finely ground stone dust) for instance. Once the cough becomes chronic (>4 weeks), occurs in the stable (e.g., at feeding, during barn checks), or persists during a workout, it is more likely to reflect IAD.

If any question exists whether infection plays a role, however, it is advisable to obtain a TTA. This is particularly true if more than one horse in the stable is affected, hematologic abnormalities are present, profuse ocular or nasal discharges are compatible with infection, or horses lack immunization. In the absence of respiratory infection, IAD is better approached with BAL and pulmonary function tests. In these horses, BAL has revealed varying increases in mast cells (>2%), neutrophils (>5% but <25%), and eosinophils (>1%).

Differential counts are easy to make using commercial stains such as Diff-Quik, but special stains (toluidine blue, May-Grünwald) may be necessary to clearly visualize mast cells. Some horses demonstrate a surprisingly high load of neutrophils (>25%) similar to that observed with heaves, without any history or signs of heaves. Whether some of these horses would later develop heaves without proper attention is controversial. On pulmonary function tests, sport horses with persistent cough have airway obstruction

that involves small airways and moderate to severe airway hyperreactivity. The airway hyperreactivity is related closely to the physiologic basis for coughing, that is, the airways have an exaggerated bronchoconstrictive response to foreign antigens or allergens that results in narrowing of the airways, mucus accumulation, and a stimulation of irritant receptors and cough.

An association between the percent mast cells in BAL fluid and airway reactivity has been made. Larger numbers of mast cells are present in horses fed dry hay when compared with soaked hay or alternative feedstuffs. This suggests that this form of IAD is allergic in origin and involves the fixation of allergen fractions on the surface of mast cells that subsequently degranulate, releasing bronchoconstrictive, proinflammatory, and growth-promoting mediators. Treatment with antihistamines alone is unsatisfactory because of the myriad of mediators involved. Use of bronchodilators is palliative at best, allowing the inflammatory process to continue unabated. Therefore steroids are recommended to reverse the pathogenesis of IAD (see Chapter 8.4: "Heaves (Recurrent Airway Obstruction): Practical Management of Acute Episodes and Prevention of Exacerbations" and Chapter 8.10: "Use of Aerosolized Bronchodilators and Corticosteroids").

### SPORT HORSES WITH EXERCISE INTOLERANCE (WITH OR WITHOUT COUGH)

This relatively common problem stems from advanced airway obstruction associated with IAD. The signs are sport-specific. The dressage horse shows lack of impulsion, lethargy, or unwillingness to flex or bend the head. The problem appears often to be seasonal (spring and summer in northeastern United States) or associated with movement to a new geographic location.

Similar effects of movement on the severity of asthma in children have been reported. Refusal or reluctance to perform advanced work that requires greater collection typically is associated with this problem. Behavioral avoidance patterns can develop that reflect poorly on the horse and rider's ability. Because these horses are often slightly older, laryngeal hemiplegia may be a complication. Therefore performance of endoscopy is important, including nasal occlusion and slap tests and inspection of the trachea for secretions.

In the event horse, IAD may manifest as a decline in stamina, early fatigue, refusal of jumps, poor heat tolerance, or exaggerated recovery from exercise. The problem of exercise intolerance is apparent in barrel racers, endurance competition horses, cutting horses, show jumpers, sprinters, carriage driving horses, and horses employed for police or military work. A keen rider notices a change in demeanor early in the course of IAD, particularly where function is compromised. When exercise intolerance occurs, a BAL and/or pulmonary function tests are recommended.

In a group of horses with poor performance but no overt signs of respiratory disease that were referred to Tufts University, the prevalence of IAD—defined as abnormal BAL, airway obstruction, and airway hyperreactivity—was more than 20%. In horses with respiratory signs including cough, mucus in the airways, the prevalence of IAD was found to be higher: more than 50%. Therefore IAD contributes to a large



percentage of performance-related problems and should be included in the differential diagnosis of any horse of any age that is performing under expectations. Screening pulmonary function tests permit rapid exclusion of IAD. In the future, it will be feasible to implement these screening tests in practice to diagnose IAD as early as possible.

In conclusion, IAD has many names, faces, and interpretations at present. IAD manifests as a constellation of clinical signs difficult to interpret in terms of functional significance. At the same time, IAD is a major cause of poor performance even in horses without respiratory signs. Diagnosing the problem as quickly as possible is vital. Also important is development of an understanding of the functional significance of findings by questioning the trainer or rider about performance. In cases of poor performance, IAD is a likely culprit, but the functional aspect requires further confirmation. In the future, pulmonary function tests in the field may provide the answer to that final riddle.

### Supplemental Readings

- Christley RM, Hodgson DR, Rose RJ et al: Coughing in thoroughbred racehorses: risk factors and tracheal endoscopic and cytological findings. *Vet Rec* 2001; 148:99-104.
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- Viel L: Small airway disease as a vanguard for chronic obstructive pulmonary disease. *Vet Clin North Am Large Anim Pract* 1997; 13:549-560.

## CHAPTER 8.4

# Heaves (Recurrent Airway Obstruction): Practical Management of Acute Episodes and Prevention of Exacerbations

JEAN-PIERRE LAVOIE

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**H**eaves, also known as *recurrent airway obstruction* (RAO) and *chronic obstructive pulmonary disease* (COPD), is an inflammatory condition in horses that results from the inhalation of dust in moldy hay and bedding. The condition affects primarily the small airways of horses and causes bronchospasm, bronchial hyperresponsiveness, mucus plugs, and pathologic changes of the bronchiolar walls, leading to obstruction of terminal airways. The mechanisms by which dust inhalation causes lower airway inflammation remains ill-defined, although evidence exists that a hypersensitivity reaction to specific antigens present in hay may be implicated. However, a wide range of particles is present in the horse's environment that also could be implicated in the development of heaves.

The treatment of heaves aims at (1) preventing further inhalation of offending dust in hay, (2) decreasing in-

flammation of the lower airways, and (3) providing symptomatic relief of airway obstruction. Although environmental dust control is pivotal to prevent the exacerbation of heaves, medications often are required for immediate improvement of airway function.

It is currently unknown whether a mechanistic relationship exists between heaves and inflammatory airway disease (IAD) in young performing horses and therefore findings regarding the treatment of heaves may not necessarily be appropriate for IAD.

### ACUTE EPISODES

The primary goal of therapy during acute exacerbation of heaves is to relieve airway obstruction primarily by the administration of antiinflammatory agents and bronchodilators.



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In conclusion, IAD has many names, faces, and interpretations at present. IAD manifests as a constellation of clinical signs difficult to interpret in terms of functional significance. At the same time, IAD is a major cause of poor performance even in horses without respiratory signs. Diagnosing the problem as quickly as possible is vital. Also important is development of an understanding of the functional significance of findings by questioning the trainer or rider about performance. In cases of poor performance, IAD is a likely culprit, but the functional aspect requires further confirmation. In the future, pulmonary function tests in the field may provide the answer to that final riddle.

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### ACUTE EPISODES

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## Corticosteroids

Corticosteroids are the most potent drugs currently available for the treatment of heaves (Table 8.4-1). The mechanisms of action of corticosteroids include decreasing smooth muscle contraction and epithelial damage by inhibiting the effects of inflammatory cells and their mediators, potentiation of the bronchodilating effects of catecholamines and reduction of mucus production. Corticosteroids with potent antiinflammatory effects are also more likely to result in detrimental effects. Corticosteroids have been commonly administered systemically, and more recently, by inhalation. An advantage of inhaled medication is achievement of a high local concentration of drug in the lungs while minimizing systemic effects. A number of corticosteroid drugs have been proposed for the treatment of heaves but objective information concerning their comparative efficacy and toxicity is sparse. Drug selection depends on the severity of the clinical signs and the ability to improve the environment. The minimal effective dose should be used, and the prolonged systemic administration of corticosteroids usually is avoided to prevent side effects.

### Systemic Corticosteroids

Systemic corticosteroid administration for a minimum of 2 weeks usually is recommended for the control of heaves. A delay of a week can be expected between the initiation of therapy and the maximal clinical response, although some improvement may be observed within a few days of drug administration. Therefore in horses with severe respiratory dysfunction, corticosteroids should be combined with drugs such as bronchodilators, which can provide symptomatic relief more rapidly. If concurrent environmental control is not performed, the respiratory signs are likely to recur soon after cessation of drug administration. For a severe attack, dexamethasone (initial dose 0.05-0.1 mg/kg, IV, followed by decremental doses and alternate day dosing) has proven efficacious to control clinical signs.

Isoflupredone acetate has the advantage that it can be administered by the intramuscular route and is as effective as dexamethasone in improving the airway function of horses with heaves. The dose used is 10 to 14 mg intramuscularly daily for 5 days; the drug is then administered on alternate days and tapered to a low dose over a period of 10 to 20 days. Although hypokalemia may occur after the administration of isoflupredone acetate to horses, the severe hypokalemic myopathy reported in cattle and in people apparently does not occur when this drug is used in horses.

Triamcinolone acetonide (20-40 mg IM) also reverses clinical signs of airway obstruction in horses with severely impaired airway function. Because long-acting corticosteroids are more likely to be associated with detrimental side effects, triamcinolone administration is recommended when short-acting corticosteroids cannot be administered. Even in severe cases when no improvement has been made in the horse's environment, the clinical improvement lasts up to 5 weeks.

Prednisone and prednisolone are less potent and less toxic than the above corticosteroids and have been used for the treatment of mildly affected horses. Recent studies have shown that oral prednisone is absorbed poorly in

Table 8.4-1

### Medications Recommended for the Treatment of Heaves

Medication	Dosage*
<b>Corticosteroids</b>	
dexamethasone	20-50 mg† IV, IM, or PO q24h
dexamethasone 21-isonicotinate	0.04 mg/kg IM q3d
prednisolone	2.2 mg/kg PO q24h
isoflupredone acetate	10-14 mg† IM q24h
triamcinolone acetonide	20-40 mg† IM
beclomethasone dipropionate	3500 µg/horse q12h in MDI (Equine AeroMask‡)
	1320 µg/horse q12h in MDI (3M Equine Aerosol Delivery System§)
fluticasone propionate	2000 µg/horse q12h in MDI (Equine AeroMask)
<b>Bronchodilators</b>	
clenbuterol	0.8-3.2 µg/kg orally twice daily
	0.8 µg/kg IV
aminophylline	5-10 mg/kg orally or IV twice daily
fenoterol	1-2 mg/horse in MDI (Equine AeroMask)
albuterol	0.8-2 µg/kg in MDI
ipratropium bromide	2-3 µg/kg q6h with mechanical nebulizer
	90-180 µg/horse q6h in MDI (Equine AeroMask)
	1200 µg/horse q6h with DPI
salmeterol	63-210 µg q8h (Equine AeroMask)
<b>Cromones</b>	
sodium cromoglycate	80 mg/horse q24h for 4 days with a mechanical nebulizer
	200 mg/horse q12h in MDI (Equine AeroMask)
nedocromil sodium	10-20 mg q8h in MDI (Equine AeroMask)

IV, Intravenous; IM, intramuscular; MDI, metered-dose inhaler; q12h, every 12 hours; DPI, dry powder inhaler.

\*Suggestive dosages are indicative only.

†The usual dose for a horse that weighs 450 to 500 kg.

‡Equine AeroMask, Trudell Medical International, London, Ontario, Canada.

§3M Equine Aerosol Delivery System, Torpex, Boehringer-Ingelheim Vetmedica, Inc., St. Joseph, Mo.

horses and, when administered in conjunction with environmental changes, provides no additional benefit over management alone.

### Inhaled Corticosteroids

Inhalation therapy is well-suited to corticosteroid administration because of the large number of glucocorticoid receptors at the level of bronchial epithelial cells and vascu-

lar endothelial cells. Inhalation therapy allows a maximal concentration of drug at the effector sites and minimizes side effects. Inhaled corticosteroids may therefore be preferable when prolonged therapy would be required.

Beclomethasone dipropionate (BDP) in metered-dose inhalers (MDIs) improves respiratory mechanics parameters within 3 to 4 treatment days. The maximal beneficial effects usually are observed during the first week of therapy. Fluticasone propionate (FDP) administered from a MDI and a mask also results in a decrease in airway obstruction, in neutrophil counts, in bronchoalveolar lavage fluid, and in bronchial hyperresponsiveness.

The information available to date in horses suggests that the short-term administration of inhaled corticosteroids is both efficacious and well tolerated but has little residual effect when the treatment is discontinued. Because a delay in response is expected with inhaled corticosteroids, they should be combined with faster acting drugs, such as bronchodilators or systemic corticosteroids in horses with respiratory distress. Bronchodilator administration also may improve pulmonary distribution of aerosolized surface-active antiinflammatory preparations. Masks used in combination with MDIs or dry powder inhalers (DPIs) increase the resistance to airflow and therefore may not be suitable and well tolerated for the initial treatment of horses with labored breathing. This author has treated a few horses that became reluctant to inhale the medication after a few days. Replacing the poorly tolerated drug with another of the same class often corrects this problem.

Chronic airway inflammation in heaves results in airway remodeling. The dosages and duration of corticosteroid administration required to restore the normal lung morphology in heaves are unknown but are likely to exceed, by far, the usually recommended posology.

Side effects of corticosteroids are uncommon based on the available literature. Detrimental findings that have been reported after systemic corticosteroid administration to heaves-affected horses include laminitis, suppression of the hypothalamo-pituitary-adrenal axis, altered bone metabolism, and bacterial pneumonia. To date, the only side effect attributed to inhaled corticosteroids is a decrease in serum cortisol.

## Bronchodilators

Bronchodilators are used in heaves-affected horses to relieve the obstruction of the small airways caused by airway smooth muscle contraction (see Table 8.4-1). Bronchodilator administration should be combined with strict environmental dust control and corticosteroid administration because inflammation of the lower airways may progress despite the improvement of clinical signs observed with drugs. Because of their rapid onset of action, bronchodilators are particularly helpful when immediate relief of clinical signs is required. The administration of bronchodilators to heavy horses may worsen hypoxemia, before an elevation in  $P_{aO_2}$  values is observed. Although this rarely appears to lead to clinical problems, combining inhaled bronchodilators with intranasal  $O_2$  insufflation in horses with respiratory distress may be advisable. The agents most commonly used for bronchodila-

tion in horses are  $\beta_2$ -adrenergic agonists and xanthine derivatives.

Clenbuterol (Ventipulmin), a  $\beta_2$ -adrenergic agonist, has bronchodilator effects and increases mucociliary transport. Side effects such as tachycardia and sweating rarely are seen with lower oral doses but are more frequent with intravenous administration. The clinical efficacy of clenbuterol at the lower recommended dosage (0.8  $\mu\text{g/kg}$  q12h) in horses with heaves is inconsistent, if exposure to dusty hay and bedding is maintained. With higher dosages (up to 3.2  $\mu\text{g/kg}$ ) the efficacy of clenbuterol improves, but so does the frequency and severity of the side effects. Fenoterol, albuterol, pirbuterol, and salmeterol are other  $\beta_2$ -agonist agents with potent bronchodilator effects that can be administered by inhalation. With inhaled  $\beta_2$ -agonist agents, bronchodilation is rapid and side effects are minimal but, with the exception of salmeterol, beneficial effects are short lived and therefore require frequent drug administration.

Because of their potentially severe side effects, anticholinergic drugs generally are not administered systemically for the treatment of heaves. Ipratropium bromide can be administered safely by aerosol, but its effects are short lived. The use of sympathomimetic agents such as ephedrine, which stimulate both  $\alpha$  and  $\beta$  receptors, has decreased because of the availability of more specific  $\beta_2$ -adrenergic agonists.

Aminophylline (Cyanamid) and pentoxifylline are methylxanthine derivatives with nonspecific phosphodiesterase inhibitory properties. Phosphodiesterase (PDE) is a family of enzymes that catalyzes the hydrolysis of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) and thereby terminates their role as second messengers in mediating cellular responses to various hormones and neurotransmitters. Activation of cAMP PDE may be a common mechanism to facilitate proinflammatory effects of cytokines and other proliferative agents. Aminophylline is used primarily as a bronchodilator in horses, but it also enhances mucociliary clearance, respiratory drive, and contractility of the diaphragm and modulates immune function. Side effects such as excitability, tachycardia, muscular tremors, and sweating are commonly observed. Because of their low therapeutic index, the use of aminophylline and other salts of theophylline are commonly preferred.

Pentoxifylline currently is approved in some countries for the treatment for navicular disease in horses. It also has bronchodilating properties, inhibits neutrophil recruitment to inflammatory sites, and at high concentration is a potent inhibitor of tumor necrosis factor (TNF)- $\alpha$  production. High dosage of pentoxifylline (16 g/horse, q12h) has been shown to be as beneficial as atropine for the relief of airway obstruction. However, oral absorption is variable and the efficacy of more practical lower dosages should be assessed.

Selective PDE inhibitors, particularly of the PDE4 subtypes, have been studied for the treatment of lower inflammatory airway diseases in people owing to the expression of PDE4 in airway smooth muscle, pulmonary nerves, and almost all inflammatory and immune cells relevant to the pathogenesis of asthma. A selective PDE4 inhibitor is effective at inhibiting the *ex vivo* production of inflammatory

mediators by equine leukocytes but fails to be effective for the treatment of horses affected with heaves.

Of the various mediators known to be involved in lung inflammatory diseases, leukotrienes are considered to be among the most important. Leukotrienes are metabolites of the arachidonic acid produced via the 5-lipoxygenase (5-LO) enzyme and its essential cofactor, the 5 lipoxygenase-activating-proteins (FLAP). Cysteinyl leukotrienes (LTC<sub>4</sub>, LTD<sub>4</sub>, LTE<sub>4</sub>) are potent bronchoconstrictors that also increase the airway vascular permeability and mucus production. However, inhibition of leukotriene synthesis or antagonists of LTD<sub>4</sub> receptors is not effective for the treatment of heaves.

### **Expectorant, Mucolytic, and Mucokinetic Agents**

Expectorants are drugs that increase pulmonary secretion, whereas mucolytic agents loosen secretions. The term *mucokinetic agent* may be preferred because it indicates that the therapy is aimed at increasing the clearance of the respiratory tract secretions. Although the administration of mucokinetic agents may help loosen the secretions in the large airways, evidence of their efficacy in improving the clinical signs of heaves is sparse. Clenbuterol, because of its bronchodilator and mucokinetic properties, may be preferred to clear mucus from the airways. Dembrexine (Sputolysin) and potassium iodide also improve clearance of bronchial secretions. Potassium iodide should be administered with caution to heavy horses because it is irritating for the respiratory tract and can induce or worsen bronchospasm. Nebulization with N-acetylcysteine (1 g/horse q12h via mechanical nebulizer) depolymerizes mucus by breaking disulfide bridges between macromolecules and has been advocated in the treatment of horses.

Overhydration by the massive administration of isotonic saline solution combined with bronchodilators or mucokinetic agents has been used to treat airway obstruction of horses with heaves. Although in a controlled laboratory setting this author failed to find an improvement in the pulmonary mechanics of heaves-affected horses with overhydration alone, it occasionally was associated with improved airway function of some clinical cases particularly when heaves-affected horses were refractory to other modes of therapy including potent corticosteroids. The proposed beneficial effects of this treatment are improved mucus transport and removal of mucus plugs related to the liquefaction of excessively viscous mucus. This treatment should be administered with caution as a number of side effects, including dyspnea and colic, have been observed with its use.

Antitussive agents are rarely indicated in the treatment of equine heaves because cough is a mechanism essential for the clearance of respiratory secretions.

## **PREVENTION OF EXACERBATION**

### **Environmental Changes**

Clinical exacerbation of heaves occurs when susceptible horses are exposed to environmental dust particles. Drugs administered to heaves-affected horses will have only

transitory effects if concurrent strict dust control measures are not applied. A wide diversity of particles may be found in a barn, including molds, noxious gases, endotoxins, and other irritants. The greatest exposure to particles small enough to be inhaled deep into the lungs of horses occurs when they are eating hay. For this reason, long-term management of heaves depends primarily on the replacement of hay in the diet by non-dusty hay alternatives. The airways of heaves-affected horses are hyperreactive, and therefore any inhaled irritants also potentially could contribute to the airway obstruction in susceptible horses.

The reversal of clinical signs of heaves with strict environmental changes may take up to 3 to 4 weeks. The remission time correlates with age and the duration and severity of illness. Horses kept permanently outdoors and fed grass or other hay substitutes usually remain free of clinical signs. Horses do well when kept outdoors even in very cold conditions, as long as they have access to enough food, fresh water (heated water tub), and shelter. The replacement of hay by less dusty feed can induce clinical remission in stabled horses. Pelleted hay, hay silage, and hydroponic hay are well tolerated and free of dust. Hay soaked in water for 2 to 4 hours before feeding may control heaves in some horses, whereas in others only partial improvement often is noted. Wood shavings, shredded paper, peanut kernels, and peat moss are good substitutes for straw, although a recent study failed to find differences in airway function in heaves-susceptible horses fed silage that were bedded on good quality straw or shavings. Other commonly made recommendations include removing the horse from the stable when cleaning the box stalls and watering the aisles before sweeping to decrease the amount of dust particles suspended in air. Proper ventilation is also important, although identifying the proper ventilation system, which would minimize dust, is problematic.

### **Aerosol Medications**

Aerosol medications, in particular steroids such as BDP and FDP, are quite effective to prevent relapses, if given long term (see Chapter 8.9: "Aerosolized Drug Delivery Devices" and Chapter 8.10: "Use of Aerosolized Bronchodilators and Corticosteroids"). These drugs prevent the cascade of inflammation that is the hallmark of the allergic process and may reduce the previous remodeling of the airway (airway wall thickening via epithelial hyperplasia and goblet cell metaplasia). Although little information exists in the literature, the use of 10 puffs of BDP (84 mcg/puff) or FDP (220 µg/puff) given daily or every other day has been reported to be an effective means to prevent exacerbations during periods of susceptibility but does not replace the need for environmental changes.

Alternatively, the prophylactic administration of sodium cromoglycate (Intal, 80 mg q24h for 4 days) by inhalation in heaves-susceptible horses in clinical remission prevented the appearance of clinical signs for up to 3 weeks after they were introduced to a dusty environment. The administration of sodium cromoglycate using a dose metered inhaler and a treatment mask facilitated drug administration and therefore decreased treatment failure resulting from inadequate drug administration. A similar mast cell blocker is nedocromil sodium (Tilade) that is

given at a dose of 10 to 20 puffs (1 mg/puff) three times per day. These two mast cell blockers may be effective in preventing exacerbations in horses that do not respond to inhaled steroids, or as supplements to reduce the need for steroids. The problem with mast cell blockers is the need for large and frequent dosing.

### Supplemental Readings

Hoffman AM: Inhaled medications and bronchodilator usage in the horse. *Vet Clin North Am Equine Pract* 1997; 13:519-530.

Lavoie JP: Update on equine therapeutics: inhalation therapy for equine heaves. *Comp Cont Educ Vet Pract* 2001; 23:475-477.  
 Robinson NE: Chairperson's report: International Workshop on Equine Chronic Airway Disease, Michigan State University, 16-18 June 2000. *Equine Vet J* 2001; 33:5-19.  
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 Thomson JR, McPherson EA: Prophylactic effects of sodium cromoglycate on chronic obstructive pulmonary disease in the horse. *Equine Vet J* 1981; 13:243-246.

## CHAPTER 8.5

# Pleuropneumonia

CORINNE R. SWEENEY  
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### THORACIC ULTRASONOGRAPHY

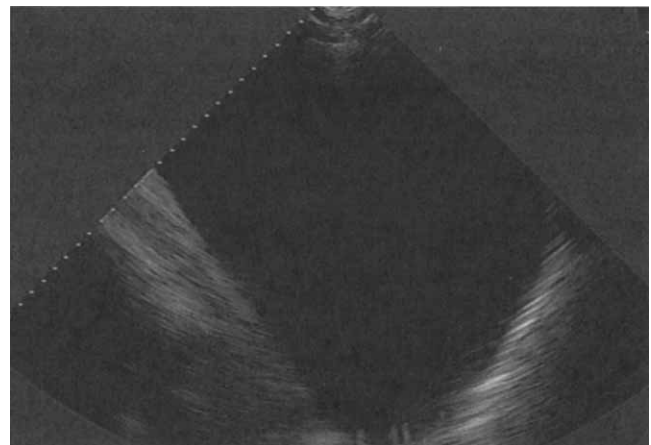
Thoracic ultrasonography currently is regarded as the preferred method to diagnose pleuropneumonia in the horse. Although the value of the art of thoracic auscultation and percussion should not be undermined, clinicians managing horses with thoracic disease recognize the limitations of these tools. With the widespread use of thoracic ultrasound, the equine practitioner currently has the ability to determine the presence of pleuropneumonia and the location and the extent of the disease. Although sector scanners are superior (preferably 3.5- to 5.0-MHz transducers), linear probes also can be used to evaluate the thorax in practice.

Thoracic ultrasonography in horses with pleuropneumonia allows the clinician to characterize the pleural fluid and to evaluate the severity of the underlying pulmonary disease. The appearance of the pleural fluid may range from anechoic to hypoechoic, depending on the relative cellularity (Figure 8.5-1). This fluid usually is found in the most ventral portion of the thorax and causes compression of normal healthy lung parenchyma with retraction of the lung toward the pulmonary hilus. The larger the volume of the effusion is, the greater the amount of compression atelectasis and lung retraction that occurs.

The presence of adhesions, pleural thickening, pulmonary necrosis, and compression atelectasis also can be detected. Fibrin has a filmy to filamentous or frondlike appearance and is usually hypoechoic (Figure 8.5-2). Fibrin deposited in layers or in weblike filamentous strands on surfaces of the lung, diaphragm, pericardium, and inner thoracic wall limits pleural fluid drainage. Dimpling of the normally smooth pleural surface results in the ap-

pearance of "comet-tail" artifacts, created by small accumulations of exudate, blood, mucus, or edema fluid. Pulmonary consolidation varies from dimpling of the pleural surface to large, wedge-shaped areas of sonolucent lung (Figure 8.5-3).

Atelectatic lung is sonolucent and appears as a wedge of tissue floating in the pleural fluid. Necrotic lung appears gelatinous and lacks architectural integrity. Peripheral lung abscesses are identified ultrasonographically by their cavitated appearance and the absence of any normal pulmonary structures (vessels or bronchi) detected within. Although detection of a pneumothorax may be



**Figure 8.5-1** Sonographic appearance of a large volume of anechoic pleural fluid.

given at a dose of 10 to 20 puffs (1 mg/puff) three times per day. These two mast cell blockers may be effective in preventing exacerbations in horses that do not respond to inhaled steroids, or as supplements to reduce the need for steroids. The problem with mast cell blockers is the need for large and frequent dosing.

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## CHAPTER 8.5

# Pleuropneumonia

CORINNE R. SWEENEY  
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### THORACIC ULTRASONOGRAPHY

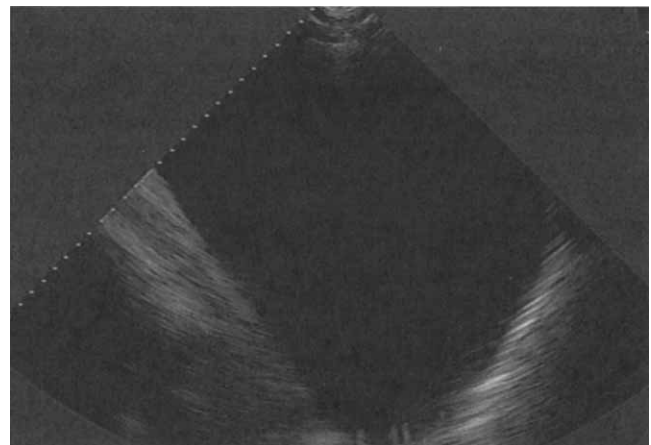
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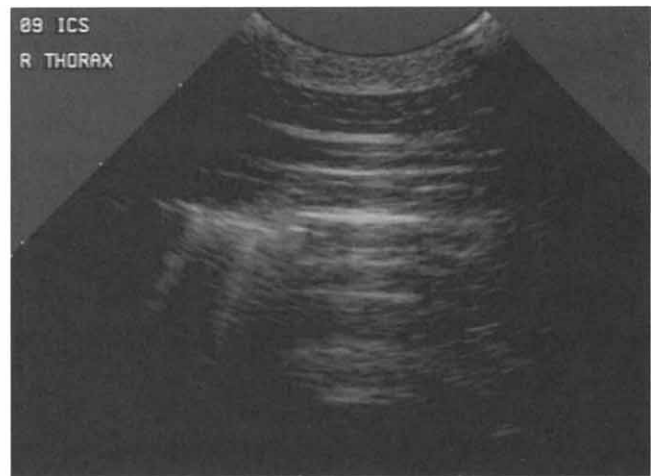
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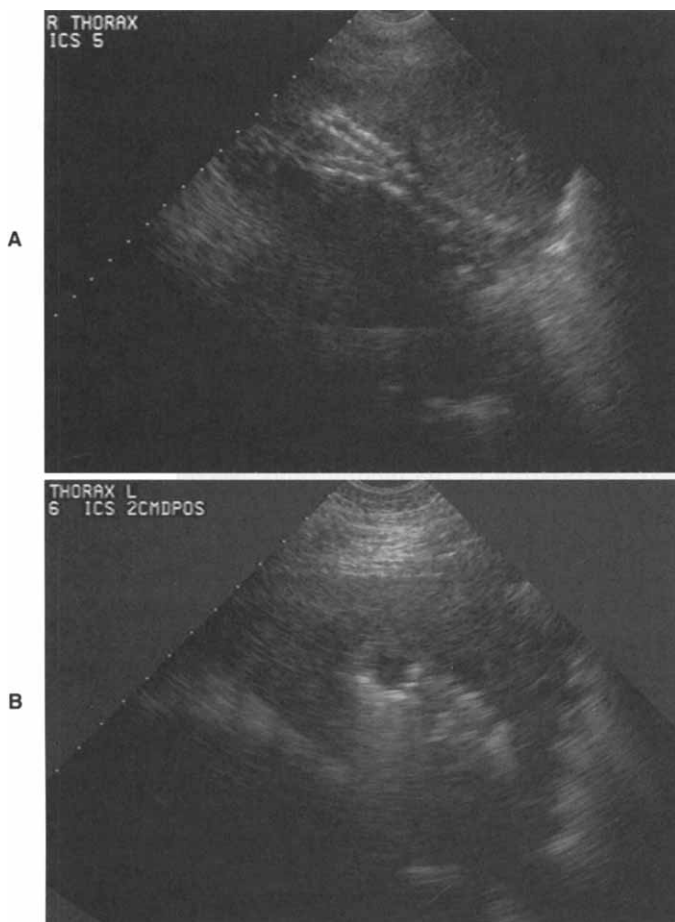
**Figure 8.5-1** Sonographic appearance of a large volume of anechoic pleural fluid.



**Figure 8.5-2** Sonographic appearance of fibrin on the visceral and parietal pleura in a horse with severe pleuropneumonia.

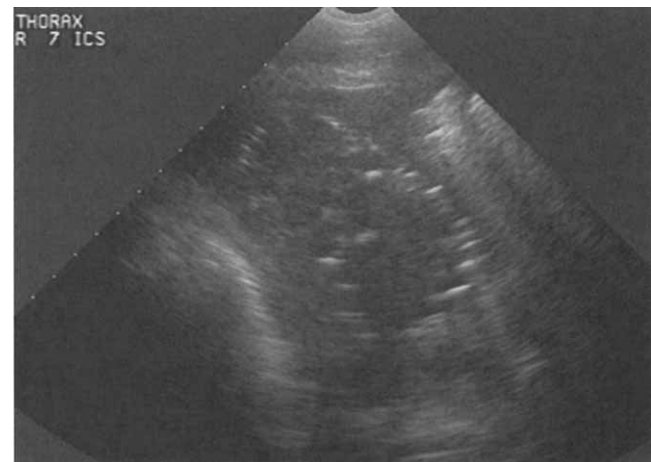


**Figure 8.5-4** Sonographic appearance of pneumothorax.



**Figure 8.5-3** **A**, Sonographic appearance of pulmonary consolidation with fluid bronchogram. **B**, Pulmonary consolidation with abscess in a horse with anaerobic pleuropneumonia.

easy for the experienced ultrasonographer, it is not as easy for the less experienced. The gas-fluid interface can be imaged through simultaneous movement in a dorsal to ventral direction with respiration, the “curtain sign” reproducing the movements of the diaphragm (Figure



**Figure 8.5-5** Sonographic appearances of free gas echoes within the pleural fluid of horse with severe pleuropneumonia.

8.5-4). The dorsal air echo moves ventrally during inspiration, similar to the lowering of a curtain, gradually masking the underlying structures. A pneumothorax without pleural effusion is even more difficult to detect ultrasonographically. Although free bright gas echoes within the pleural fluid can occur after thoracentesis, they are more often seen with anaerobic infections or when sufficient necrosis has occurred in a segment of parenchyma to erode into an airway and form a bronchopleural fistula (Figure 8.5-5). The absence of gas echoes in pleural fluid does not rule out the possibility that anaerobic infection may be present.

Ultrasonography is a valuable diagnostic aid in the evaluation of the pleura, lung, and mediastinum of horses with pleuropneumonia. The detection and further characterization of the above abnormalities improve the clinician’s ability to form a more accurate prognosis. Adhesions can be detected that ultimately may affect the horse’s return to its previous performance level.

Horses with compression atelectasis and a nonfibrinous



pleuritis have an excellent prognosis for survival and return to performance. The detection of areas of consolidation, pulmonary necrosis, or abscesses increases the probable treatment and recovery time, and the prognosis for survival decreases as these areas become more extensive. Ultrasonography can be used as a guide to sample or drain the area with a large fluid accumulation or the least loculation. These patients often benefit from progressive scanning to assess response to treatment and the need for drainage.

## PLEURAL DRAINAGE

After selection of an appropriate antimicrobial agent, the next decision to be made is whether to drain the pleural space. Ideally the decision is based on an examination of the pleural fluid. If the pleural fluid is thick pus, drainage using a chest tube should be initiated. If the pleural fluid is not thick pus, but the Gram's stain is positive and white blood cell (WBC) counts are elevated, pleural drainage is recommended. Another indication for therapeutic thoracocentesis is the relief of respiratory distress secondary to a pleural effusion.

Many options exist for thoracic drainage, including intermittent chest drainage, use of an indwelling chest tube, pleural lavage, pleuroscopy and debridement, open chest drainage/debridement with or without rib resection in the standing horse, open chest drainage/debridement under general anesthesia, and lung resection under general anesthesia. Drainage of a pleural effusion can be accomplished by use of a cannula, indwelling chest tubes, or a thoracostomy. Thoracostomy is reserved for severe abscessation of the pleural space. Thoracocentesis is accomplished easily in the field and may not need to be repeated unless considerable pleural effusion reaccumulates.

Indwelling chest tubes are indicated when continued pleural fluid accumulation makes intermittent thoracocentesis impractical. If properly placed and managed, indwelling chest tubes provide a method for frequent fluid removal and do not exacerbate the underlying pleuropneumonia or increase the production of pleural effusion. The chest entry site and end of the drainage tube must be maintained aseptically. A one-way flutter valve may be attached to allow for continuous drainage without leakage of air into the thorax. If a chest tube is placed aseptically and managed correctly, it can be maintained for several weeks. It should be removed as soon as it is no longer functional. Heparinization of tubing after drainage helps maintain patency. Local cellulitis may occur at the site of entry into the chest but is considered a minor complication. Bilateral pleural fluid accumulation requires bilateral drainage in most horses.

Open drainage or thoracostomy may be considered when tube drainage is inadequate. Open drainage should not begin too early in the disease. An incision is made in the intercostal space exposing the pleural cavity and causing a pneumothorax. If the inflammatory process has fused the visceral and parietal pleura adjacent to the drainage site, a pneumothorax may not develop. The wound is kept open for several weeks while the pleural space is flushed and treated as an open draining abscess.



**Figure 8.5-6** Chest tube drainage of pleural fluid in horse with severe pleuropneumonia.

## PLEURAL LAVAGE

Pleural lavage may be helpful to dilute fluid and remove fibrin, debris, and necrotic tissue. Lavage apparently is most effective in subacute stages of pleuropneumonia before loculae develop; however, pleural lavage may help break down fibrous adhesions and establish communication between loculae. Care must be exercised that infused fluid communicates with the drainage tube. Lavage involves infusing fluid through a dorsally positioned tube and draining it through a ventrally positioned tube (Figure 8.5-6). In addition, 10 L of sterile, warm lactated Ringer's solution is infused into each affected hemithorax by gravity flow. After infusion, the ventrally placed chest tube is opened and the lavage fluid is allowed to drain. Pleural lavage probably is contraindicated in horses with bronchopleural communications because it may result in spread of septic debris up the airways. Coughing and drainage of lavage fluid from the nares during infusion suggest the presence of a bronchopleural communication.

## DIFFERENTIATION FROM NEOPLASIA

Although pleuropneumonia is the most common cause of pleural effusion in the horse, the second most common cause is neoplasia. Differentiating between the two conditions is a challenge for the equine clinician because similarities exist in the clinical signs and physical examination findings.

Pleuropneumonia effusions are more likely to have abnormal nucleated cell count more than 10,000/ $\mu$ l (usually >20,000/ $\mu$ l) with greater than 70% neutrophils. Bacteria frequently are seen both intra- and extracellularly. A putrid odor may be present.

Neoplastic effusions have variable nucleated cell count. If caused by lymphosarcoma, abnormal lymphocytes may



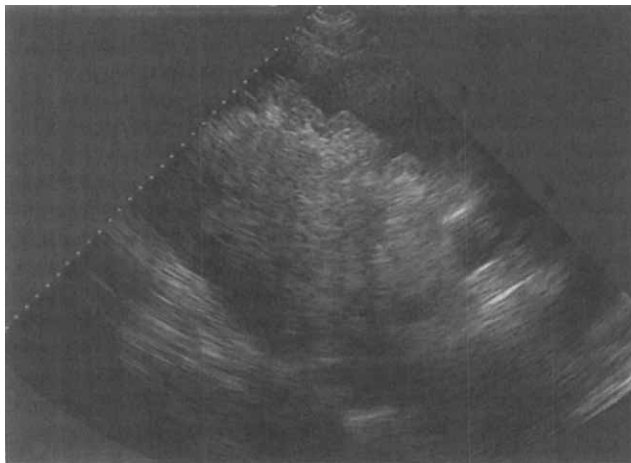
predominate. However, neoplastic cell often are not readily apparent and a definitive diagnosis may be difficult. Rarely do neoplastic effusions have a putrid odor. Bacteria are seen rarely in the cytology preparations.

Once again, use of ultrasonography helps determine if neoplasia is responsible for the effusion. Fibrin most commonly is detected in association with pleuropneumonia but has been detected in horses with thoracic neoplasia. Mediastinal masses associated with neoplasia may be readily visible (Figure 8.5-7). Abnormal solitary masses on the lung surface may be visible in horses with meta-static neoplastic disease.

### COMPREHENSIVE MANAGEMENT

The primary goals in managing a horse with pleuropneumonia are to stop the underlying bacterial infection, remove the excess inflammatory exudate from the pleural cavity, and provide supportive care. Ideally an etiologic agent is identified from either the tracheobronchial aspirate or pleural fluid and antimicrobial sensitivity determined. Without bacterial culture results, broad-spectrum antibiotics should be used because many horses have mixed infections of both gram-positive and gram-negative and aerobic and anaerobic organisms. Commonly used therapy is penicillin combined with an aminoglycoside such as gentamicin, enrofloxacin, trimethoprim and sulfamethoxazole, or chloramphenicol. Because of the need for long-term therapy, initial intravenous or intramuscular antimicrobials may need to be followed by oral antimicrobials. Preferably the oral antimicrobials are not administered until the horse's condition is stable and improving because blood levels obtained by this route are not as high as those achieved by use of intramuscular or intravenous administration.

Treatment of anaerobic pleuropneumonia is usually empiric because antimicrobial susceptibility testing of anaerobes is difficult due to their fastidious nutritive and atmospheric requirements. Thus familiarity with antimicrobial susceptibility patterns is helpful in formulating



**Figure 8.5-7** Sonographic appearance of melanoma located in the cranial mediastinum.

the treatment regimen when an anaerobe is suspected. The majority of anaerobic isolates are sensitive to relatively low concentrations (22,000 IU/kg IV q6h) of aqueous penicillin. *Bacteroides fragilis* is the only frequently encountered anaerobe that is routinely resistant to penicillin, although other members of the *Bacteroides* family are known to produce  $\beta$  lactamases and are potentially penicillin-resistant.

Chloramphenicol (50 mg/kg PO q4h) is effective against most aerobes and anaerobes that cause equine pleuropneumonia. However, because of human health concerns the availability of chloramphenicol may decrease. Metronidazole has *in vitro* activity against a variety of obligate anaerobes including *B. fragilis*. Pharmacokinetic studies indicate a dose of 15 mg/kg intravenously or orally four times a day is necessary to maintain adequate serum levels. Oral administration rapidly results in adequate serum levels and thus is an acceptable route of administration for horses with pleuropneumonia. Metronidazole is not effective against aerobes and therefore always should be used in combination therapy at a dose of 15 mg/kg every 6 to 8 hours. Side effects of metronidazole include loss of appetite and lethargy; use of the drug should be halted when these signs are observed. Aminoglycosides and enrofloxacin should not be considered for the treatment of pleuropneumonia caused by an anaerobe unless these drugs are used in combination therapy with penicillin.

### Ancillary Treatment

Antiinflammatory agents help reduce pain and may decrease the production of pleural fluid. This in turn may encourage the horse to eat and maintain body weight. Flunixin meglumine (500 mg q12-24h) or phenylbutazone (1-2 g q12h) is commonly used for this purpose. In this author's opinion, corticosteroids are contraindicated for the treatment of bacterial pleuropneumonia. Rest and the provision of an adequate diet are important components of the treatment of pleuropneumonia. Because the disease course and period of treatment are usually prolonged, attempts should be made to encourage eating. Intravenous fluids may be indicated in the acute stages of the disease to treat dehydration resulting from anorexia and third-space losses into the thorax.

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## CHAPTER 8.6

# Interstitial Pneumonia

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**I**nterstitial pneumonia is an uncommon cause of acute or chronic disorders of the lower respiratory tract of horses. However, because of the severity of the process, recognition and definitive diagnosis of this entity are important as early as possible in its clinical course.

The term *interstitial pneumonia* defines a number of diseases that are chronic and progress to pulmonary fibrosis. The course is insidious and morphologically characterized by alveolar structural derangements that lead to loss of functional gas exchange units of the lung and altered mechanical properties of the lung, characterizing the pneumonia as a restrictive lung problem.

### ETIOLOGY

Multiple agents have been implicated in the genesis of interstitial pneumonia in animals, but fewer than 20 have been confirmed in horses. Chief among these are infectious agents and ingested toxins. Frequently the etiologic agent cannot be identified because of the insidious nature of the process, and the final diagnosis is idiopathic interstitial pneumonia. The lung responds in a rather stereotypic manner to injury and our limited ability to identify infectious, toxic, and immunologic causes frequently hinder current ability to make an accurate identification of a specific etiology. All efforts should be made to identify an etiologic agent early in the course of the disease, but the practitioner needs to be aware that treatment frequently is nonspecific and supportive. Agents representing all major etiologic categories of disease can cause interstitial pneumonia (Box 8.6-1).

### Infectious Agents

Infectious causes of interstitial pneumonia in horses and foals include viral, bacterial, parasitic, protozoal, and fungal agents. Typically the pneumonia is acute and severe, characterized by severe damage to the lung parenchyma (alveolar region).

Viral agents frequently are implicated or suspected but rarely identified by the usual serologic, histopathologic, and virus isolation methods. The advent of more sensitive and specific techniques, such as *in situ* polymerase chain reaction (PCR) and monoclonal antibody immunohistochemistry (IHC), may partially resolve the current diagnostic challenge. Equine influenza virus, equine arteritis virus, equine herpes virus type 1 and 4, and Morbillivirus have been demonstrated as etiologic agents of interstitial pneumonia in horses and foals. Interstitial pneumonia caused by viruses must be distinguished from the more typical

### BOX 8.6-1

#### Causes of Interstitial Pneumonia in Horses

##### Acute

Infections (systemic viral, bacterial, parasitic)

Inhaled chemicals

Oxygen ( $\text{FiO}_2 > 50\%$ )

Smoke

Ingested toxins or precursors

Perilla mint (*Perilla frutescens*), crofton weed (*Eupatorium adenophorum*), *Crotalaria* spp., *Senecio* spp.

Adverse drug reactions

Uncertain

Hypersensitivity

Acute hypersensitivity pneumonitis

Endogenous metabolic/toxic conditions

Shock, particularly endotoxic (ARDS)

DIC

Uremia

Idiopathic/cryptogenic causes

##### Chronic

Infections (systemic viral, bacterial, parasitic)

Inhaled inorganic dust (pneumoconioses)

Silicosis

Hypersensitivity

Hypersensitivity pneumonitis

Ingested toxins or precursors

Perilla mint (*Perilla frutescens*), crofton weed (*Eupatorium adenophorum*), *Crotalaria* spp., *Senecio* spp.

Collagen-vascular disorders

Uncertain

Idiopathic/cryptogenic causes

ARDS, Acute respiratory distress syndrome; DIC, disseminated intravascular coagulation.

bronchointerstitial pneumonia. Uncomplicated viral pneumonia is centered on the bronchioles and adjacent alveolar parenchyma and is termed *bronchopneumonia* by the pathogenetic pattern. Although interstitial accumulation of lymphocytes, plasma cells, and macrophages rapidly becomes the dominant feature of the lesion, the response clearly is associated with bronchioles and associated alveoli and the term *bronchointerstitial pneumonia* is suitable.

Evaluation of whether or not the parenchymal abnormality is centered on bronchioles is one of the most

important criteria in the histologic diagnosis and interpretation of pulmonary parenchymal disease. The pattern of pneumonia resulting from inhaled viral pathogens is dependent on the tropism of the virus and the extent to which viral replication is limited by the host immune system, in part determined by the genetic constitution of the host. Pneumonia in the horse can originate from viremia, with the pulmonary endothelial cells being the primary site of viral replication, such as is seen in the pulmonary vasculotropic form of equine herpes virus infection. The interstitial pneumonia resulting from this form of EHV-1 and from EVA in foals and adults has been well described, as has pneumonia associated with Morbillivirus (Hanta virus) in horses. Influenza occasionally produces severe interstitial pneumonia in humans, and although not described in the horse as a specific entity, this may be the case in some individuals. Follow-up of human cases has revealed interstitial fibrosis as a long-term problem after influenza interstitial pneumonia. Apparently in the horse, virus-associated interstitial pneumonia most commonly is associated with viruses having tropism for vascular endothelial cells and that interstitial pneumonia follows viremia, rather than direct infection of the airway epithelium.

In some horses with bronchointerstitial pneumonia of unknown cause, bacterial agents have been isolated from the lung. The usual distribution of bacterial bronchopneumonia in the horse is cranioventral, whereas the distribution in interstitial pneumonia is diffuse. In the latter cases the bacteria are most likely opportunistic pathogens and do not represent the primary causative agent. An exception is *Rhodococcus equi* pneumonia of foals, which can cause an acute respiratory distress syndrome in older foals. *R. equi* has been cultured from foals with severe, acute bronchointerstitial pneumonia with a diffuse pulmonary distribution. Interstitial pneumonia associated with *Pneumocystis carinii* has been described in the foal and *Mycoplasma* spp. has been isolated from the respiratory tract of adult horses. The significance of the *Mycoplasma* spp. isolates remains a matter of debate. *P. carinii* pneumonia is thought to occur primarily in immunocompromised foals as a complication of some other serious disease, such as infectious pneumonia or severe combined immunodeficiency (SCID). It is characterized by plasmacytic lymphocytic interstitial pneumonia with flooding of alveoli with foamy acidophilic material.

Parasitic pneumonia, an uncommon cause of chronic bronchointerstitial pneumonia, usually occurs in young foals secondary to migration of *Parascaris equorum* larvae through the pulmonary parenchyma. In adult horses, *Dictyocaulis imfeldi* is the cause of lungworm infection. Direct exposure to donkeys, the natural host of the parasite, is usually present in the history; however, documented cases of lungworm exist where no known association with donkeys was present. Fungal infections resulting from *Aspergillus* spp., *Cryptococcus* spp., and *Histoplasma* spp. result in severe chronic pyogranulomatous pneumonia, primarily in immunocompromised individuals, and are often fatal.

### Ingested Chemicals

Ingested chemicals rank second only to infectious agents as potential causes of interstitial pneumonia in horses. In-

gestion of pyrrolizidine alkaloids from a variety of plants (mostly genus *Crotalaria*, *Trichodesma*, and *Senecio*) can cause interstitial pneumonia in horses. This toxicity is associated with production of a toxic metabolite activated in the liver that then circulates to the lung. The toxic alkylating agents damage capillary endothelial cells, although the amount of alkylid required to damage the lung is generally less than that required for hepatotoxicity. Crofton weed (*Eupatorium adenophorum*) a poisonous plant found primarily in Australia and Hawaii produces interstitial pneumonia in horses. Toxicity is associated with ingestion of the flowering plant, but the nature of the toxin is not known. Perilla ketone, derived from the plant *Perilla frutescens*, produces acute respiratory distress within a week of ingestion in ponies. The lesions include diffuse alveolitis and type II pneumocyte proliferation with sparing of the bronchioles. Toxicity depends on additional metabolism of the 3-substituted furan by the mixed function oxidase system, which occurs directly in the lung of the horse.

### Inhaled Chemicals

Direct pulmonary injury by inhaled chemicals is an uncommon cause of interstitial pneumonia in horses. In people, this type of pneumonia is related primarily to occupational exposure. Smoke inhalation causes acute, diffuse interstitial pneumonia in horses, frequently followed within a few days by opportunistic bacterial pneumonia. The initial damage is due to a combination of inhaled noxious gas and heat effects. Respiratory compromise after smoke inhalation initially results from loss of surfactant and epithelial cells, followed by pulmonary edema and alveolitis. Severe insults can result in pseudomembranous casts in the small airways, producing airway obstruction.

Oxygen toxicity theoretically can produce interstitial pneumonia and alveolar type II cell proliferation. This problem is more likely to be seen in neonatal foals ventilated with increased levels of oxygen ( $\text{FiO}_2 > 50\%$ ) for several days. Damage presumably is due to production of reactive oxygen metabolites, which attack a lung that already may have been injured by barotrauma, resulting from a ventilator driven increase in airway pressure. Agri-chemicals or herbicides, such as paraquat, may cause acute interstitial pneumonia in horses and should be considered in horses with a history of possible exposure. Silicosis is a specific chronic granulomatous pneumonia of horses associated with inhalation of silicon dioxide crystals. This syndrome has been described in horses originating from the Carmel Valley region of California. The inhaled particles are ingested by alveolar macrophages and result in lysis of the macrophage, chronic alveolitis, and fibrosis. Multiple granulomas are present and submicron intracytoplasmic crystalline particles can be identified in macrophages.

### Hypersensitivity Reactions

In the most specific sense, hypersensitivity pneumonitis refers to pulmonary disease caused by inhalation of organic antigens. Lymphocytic, plasmacytic bronchitis, and bronchiolitis, combined with lymphocytic interstitial

pneumonia, characterize the disease in the horse lung. Granuloma formation and fibrosis can be observed. Chicken dust and fungi have been implicated as a cause of severe, chronic bronchointerstitial pneumonia in six horses, but the syndrome itself is quite rare.

### Endogenous Metabolic and Toxic Conditions

A variety of conditions cause acute pulmonary injury with inflammatory edema or severe alveolar wall damage and serofibrinous exudation similar to that described for acute interstitial pneumonia. Acute uremia, shock, burns, and trauma can produce an acute pulmonary injury termed *acute lung injury (ALI)* or *acute respiratory distress syndrome (ARDS)*, depending on severity. Although endotoxin does not directly injure the lung, endotoxemia in the horse initiates inflammatory and metabolic cascades that can lead to pulmonary injury. Activation of these pathways produces vasoactive and chemoattractant molecules that increase vascular permeability, activate complement, produce proinflammatory cytokines, and release neutrophil enzymes that can affect the lung of horses adversely. Horses, as a species, are sensitive to the negative effects of endotoxemia and their lungs are particularly sensitive, perhaps because of the presence of intravascular macrophages, which further amplify the inflammatory cascade. Although ARDS is not yet clearly defined as a clinical entity in horses, it is likely that this underrecognized syndrome of horses is similar in underlying pathophysiology to that described in humans (Box 8.6-2).

### PATHOPHYSIOLOGY

Interstitial pneumonia progresses through four phases. During the first, the initial insult causes parenchymal injury and alveolitis. This is followed by a proliferative phase characterized by cellular and parenchymal alterations in tissues of the lung. Chronic cases progress to the development of interstitial fibrosis, whereas the final stage results in end-stage irreparable fibrosis of the lung.

The structural changes that occur in the lung reduce the number of functional alveoli, adversely affecting ventilatory function of the lung and altering ventilation/perfusion relationships. Reduced lung compliance is associated with the loss of distensible alveoli and presence of pulmonary edema and fibrosis. Total and vital lung ca-

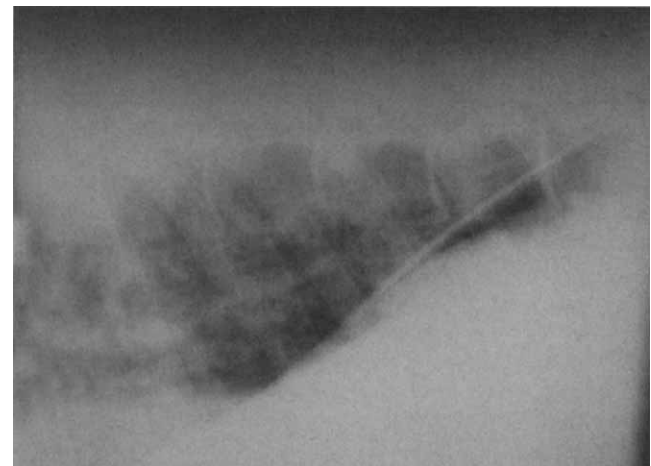
pacities are decreased in association with the loss of functional gas exchange units and reduced lung compliance. The work of breathing is increased, resulting in exercise intolerance and difficulty in breathing. Pulmonary hypertension and *cor pulmonale* may present as complications of interstitial pneumonia and fibrosis. Although the origin of pulmonary hypertension is unclear, hypoxic vasoconstriction and generation of vasoactive compounds (such as endothelin-1) that alter pulmonary vascular resistance acutely, and vessel anatomy chronically, may play a role.

### CLINICAL SIGNS

Horses affected with interstitial pneumonia frequently present with fever, cough, weight loss, nasal discharge, exercise intolerance, severe dyspnea, cyanosis, and a restrictive breathing pattern. A "heave line" is frequently present; nostril flare and an anxious expression are usual. The history can be acute or chronic. Although affected foals are frequently depressed and anorectic, adults may be bright and alert with a variable appetite. The disease proceeds toward death in many cases, with progressive respiratory compromise, although some also may improve slowly with time. More than one foal at a farm may be affected.

### DIAGNOSIS

In older horses, the primary differential diagnosis of heaves may be excluded by the leukocytosis and hyperfibrinogenemia that commonly occur in horses with interstitial pneumonia and fibrosis but do not occur in horses with heaves. However, these abnormal features are common in horses with infectious bronchopneumonia and thoracic radiography is paramount in the establishment of a definitive diagnosis. Typically, thoracic radiographs reveal extensive interstitial and bronchointerstitial pulmonary patterns (Figure 8.6-1). Nodular infiltrates



**Figure 8.6-1** Radiographic appearance of caudodorsal lung field in a horse with idiopathic interstitial pneumonia. Note the increased interstitial pattern and nodular alveolar pattern. Histopathology of a postmortem specimen from this horse is presented in Figure 8.6-2.

### BOX 8.6-2

#### Causes of Acute Respiratory Distress Syndrome

- Acute viral or bacterial pneumonia
- Septicemia, endotoxemia
- Shock, massive burns, trauma, prolonged surgery
- Aspiration of liquids
- Chemical/drug toxicity
- Uremia
- Disseminated intravascular coagulation (DIC)
- Oxygen toxicity (?)

may be present, either large or miliary, but always diffusely distributed.

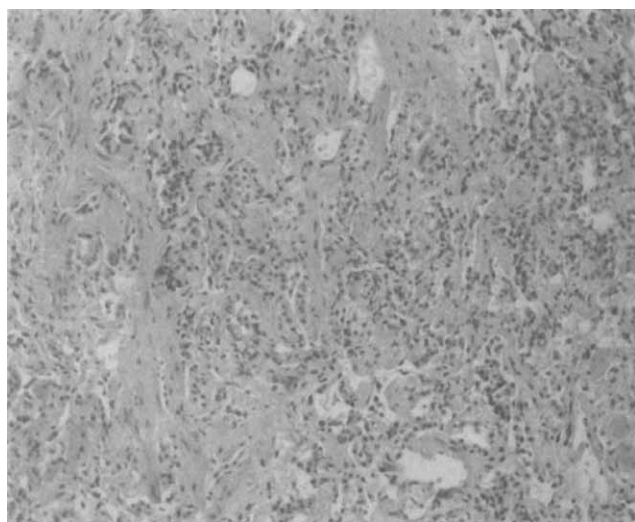
Culture of transtracheal or bronchoalveolar lavage (BAL) aspirates often yields no significant growth of bacterial or fungal pathogens. This is particularly useful in foals and, in combination with negative results of a Gram-stained tracheal aspirate, reinforces the clinical diagnosis of interstitial pneumonia. Cytologic evaluation of tracheal or BAL fluid shows increased numbers of neutrophils and macrophages. If *P. carinii* is involved, BAL fluid may reveal trophozoites or intracystic bodies with special stains, such as toluidine blue or methenamine silver.

Histologic examination of a transthoracic lung biopsy specimen is the definitive diagnostic test for chronic interstitial pneumonia and fibrosis (Figure 8.6-2). Care must be taken to ensure the biopsy is obtained from a representative area and ultrasound guidance has been useful in the hands of the author. Complications from this technique are uncommon but can occur. Biopsy rarely defines the causative agent but confirms the clinical diagnosis.

Additional diagnostics could include arterial blood gas analysis, abdominocentesis, and thoracocentesis to rule out metastatic neoplastic disease, pulmonary function testing, viral isolation, serologic testing for antibody to fungi and chicken serum if hypersensitivity pneumonitis is suspected, and immunohistochemical evaluation of lung tissue for suspected infectious agents. A complete cardiac evaluation also should be conducted to screen for pulmonary hypertension and *cor pulmonale*.

## TREATMENT

Treatment of these cases is often unrewarding. Therapeutic goals are treatment of any underlying or secondary infection; suppression of inflammation; maintenance of tissue oxygen delivery within appropriate limits; relief of any



**Figure 8.6-2** Postmortem histopathology specimen from a horse with severe interstitial pneumonia and fibrosis. Prominent alveolar septa thickening and consequent alveolar space narrowing due to progressive severe interstitial collagen deposition (fibrosis). (Courtesy Dr. Fabio Del Piero, University of Pennsylvania, New Bolton Center, Philadelphia.)

associated bronchoconstriction; and prevention or treatment of complications. Environmental control, with appropriate temperature and humidity control and good ventilation, is beneficial.

Parenteral corticosteroid therapy is the mainstay of treatment, with early and aggressive therapy providing the best long-term outcome, particularly in foals. In one report of 23 foals affected with acute bronchointerstitial pneumonia, 9 of 10 treated with corticosteroids survived, whereas none of those not receiving steroid treatment lived. Dexamethasone (0.1 mg/kg q24h) is suggested initially. Inhaled beclomethasone (8 µg/kg q12h) may be considered. Additional antiinflammatory therapy includes, but is not limited to, dimethyl sulfoxide (DMSO; 1 g/kg as a 10% solution IV q24h), flunixin meglumine (Banamine; 1 mg/kg IV q12h) and methyl sulfonyl methane (15-20 mg/kg PO q24h).

Broad-spectrum antimicrobial treatment should be instituted initially, particularly in foals, as described for the treatment of infectious bronchopneumonia (see Chapter 8.5: "Pleuropneumonia"). The choice of antimicrobial and duration of therapy should be dictated finally by the culture and sensitivity results from the transtracheal aspirate and by the patient's clinical course.

Foals, in particular, and adults with severe respiratory distress may benefit from nasal insufflation of humidified oxygen, with flow rates of 10 L/min for foals and 15 L/min in adults. If necessary, as determined by persistent hypoxemia in the face of intranasal insufflation at the rates given, a second nasal canula can be placed in the opposite nostril to increase the  $F_{IO_2}$ . Care must be taken to avoid obstruction of the nasal passages. Alternatively, intratracheal or transtracheal insufflation can be considered to further increase  $F_{IO_2}$  and improve oxygenation.

Systemic bronchodilator therapy may or may not be indicated in these cases. If utilized, bronchodilators may worsen ventilation-perfusion inequalities. Thus bronchodilator therapy should be accompanied by supplemental oxygen and the effects should be monitored with serial blood gas measurements and discontinued if hypoxemia worsens. Nebulized or aerosolized bronchodilator therapy may be more judicious, and beneficial effects are evident in some foals with respiratory distress. Examples include albuterol (180-360 µg) or ipratropium bromide (40-80 µg) or two to four puffs of either, or in combination. Aminophylline and theophylline should not be used because of their narrow therapeutic range. Furosemide (0.5 mg/kg q12h) may be appropriate for its bronchodilator effect and its effect on reducing pulmonary artery pressure, particularly if *cor pulmonale* develops. It is particularly useful in the management of pulmonary edema. Potential useful therapies in the future may include compounds such as endothelin-1 ( $ET_A$ ) receptor antagonists and inhibitors of fibrosis, such as colchicine.

## PROGNOSIS

The prognosis of interstitial pneumonia in horses is uniformly poor to guarded. Affected foals, treated early and aggressively with corticosteroid and antimicrobial therapy, have the best outlook for life. The disease is usually progressive in adults and eventually results in the demise of

the horse, although the occasional horse recovers sufficiently to return to previous performance levels. A fair number of adult horses, with continuous intense management, live for a period of time but will be severely compromised, limiting their usefulness.

Exceptions to the poor prognosis may be seen in cases of *P. carinii* pneumonia in foals if they are treated early and aggressively and in cases of idiopathic interstitial pneumonia in adult horses that are treated early with corticosteroids. A trial of treatment for peracute interstitial disease for 48 hours is warranted and chronic interstitial pneumonia should be treated for a minimum of 2 to 4 weeks before discarding the possibility of recovery.

### Supplemental Readings

Ainsworth DM, Weldon AD, Beck KA et al: Recognition of *Pneumocystis carinii* in foals with respiratory distress. *Equine Vet J* 1993; 25:103-108.

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## CHAPTER 8.7

# Exercise-Induced Pulmonary Hemorrhage

DAVID JOHN MARLIN

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In exercise-induced pulmonary hemorrhage (EIPH) blood is present in the airways after exercise. The most frequent classification of horses as EIPH positive or negative is currently based on postexercise endoscopy. Until the introduction of endoscopy and surveys of horses after racing, it generally was considered that only few horses experienced EIPH, and the occurrence was based only on the appearance of blood at the nostrils (epistaxis). Even today, the lay perception of a horse classified as a "bleeder" is frequently that of an animal that either has profuse amounts of blood in the trachea after training or racing or exhibits epistaxis.

However, EIPH should now be considered ubiquitous in horses undertaking fast or intense exercise. The range of the condition varies from horses showing only a small increase in the number of red blood cells detectable in the airways using sensitive techniques such as bronchoalveolar lavage (BAL) to those showing marked epistaxis, with all grades in between. Whether all gradations of EIPH share a common etiology is unknown.

Some debate exists as to the intensity of exercise required to induce EIPH. Hemosiderophages are present in the tracheal wash of all horses in training when galloping.

More recently, studies showed that lesions consistent with EIPH were present in the lungs *post mortem* of 10 of 13 Thoroughbred horses aged less than 2 years that had been trained at speeds of only 7 to 8.5 m/s (420-510 m/min or 16-19 mph). In addition, 100-fold increases occur in red blood cell numbers in BAL taken after treadmill exercise at only 600 m/min (22.5 mph), but without blood being present in the trachea.

Although for many years seen as a condition affecting the Thoroughbred racehorse, it is now clear that EIPH occurs in any horse undertaking fast or intense exercise, including Thoroughbred racing on turf or dirt, racing over jumps (hurdle and steeplechase), 3-day eventing, polo, barrel racing, reining, roping and cutting, Quarter Horse racing, Appaloosa racing, Arab racing, Standardbred racing (pacing and trotting), show-jumping, and even in draught and endurance horses. The greater the severity of EIPH the greater is the implication for health and welfare. In addition, moderate to severe EIPH commonly is thought to be a contributing factor in poor performance.

However, despite considerable anecdotal evidence, only one study has found that severe endoscopic EIPH was less common in placed than in unplaced horses. A

the horse, although the occasional horse recovers sufficiently to return to previous performance levels. A fair number of adult horses, with continuous intense management, live for a period of time but will be severely compromised, limiting their usefulness.

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However, despite considerable anecdotal evidence, only one study has found that severe endoscopic EIPH was less common in placed than in unplaced horses. A



recent report showed that the incidence of endoscopic EIPH in a group of 166 horses examined immediately posttrace in the United Kingdom (flat and jump racing) because of poor performance was no different than that of controls (horses performing to expectation). In addition, no relationship existed between EIPH incidence or severity and finishing position in either the control (223 horses) or poor performance group.

In most cases, EIPH affects the pulmonary circulation, although severe episodes of EIPH may involve disruption of the bronchial circulation. In 2- to 3-year-old Thoroughbred racehorses, *post mortem* examination of the lungs reveals lesions consistent with EIPH almost exclusively in the tips of the dorsocaudal lung. These may be visible on gross examination or only on histologic examination using microscopy. With increasing age, there is a pattern for the lung to be stained a dark brown-blue (because of repeated and extensive hemosiderin deposition) and for the area of lung affected to be more extensive. The areas of staining are often approximately symmetric in the left and right lung and often may extend to the most cranial regions along the medial spinal surface of both lungs.

A number of endoscopic surveys of EIPH in racehorses have described the incidence (i.e., the chance that an individual horse on a single occasion will have blood in the trachea postexercise) as being between 30% and 80%. If multiple examinations are made on the same horse, the incidence rises to 82% to 95%. The endoscopic incidence of EIPH has been shown to increase from 40% in 2-year-old Thoroughbreds racing on grass, to 65% in 3-year-olds and 82% in horses ages 4 and older.

The incidence of epistaxis associated with Thoroughbred and Arabian racing in Japan recently was reported to be 0.15%. Risk factors for epistaxis included jump-racing, age greater than 2 years, race distances of less than 1600 m (1 mile), and female gender. The recurrence rate in individual horses was relatively low (4.6%). In contrast to endoscopic EIPH and performance, externally visible epistaxis was shown to have a significant effect on the performance of Thoroughbred racehorses in Korea.

## ETIOLOGY

A number of different theories have been proposed to explain the occurrence of EIPH, however few, if any, have been able to explain the initial site of occurrence and pattern of progression of hemorrhage through the lung. The most widely accepted theory at present is that of pulmonary capillary stress failure resulting from high transmural pressures (i.e., pressures or stresses acting on the pulmonary capillaries). Pulmonary capillary transmural pressure is determined by pulmonary capillary pressure and airway pressure. The horse has high pulmonary vascular pressures during intense exercise. When the high pulmonary vascular pressures (exceeding 100 mm Hg) distending the blood vessels are opposed by high positive airway pressures, such as occur during expiration, the transmural pressure and, by implication, wall stress is low. However, when the distending internal vascular pressure coincides with a large negative airway pressure, as occurs during inspiration, the transmural pressure and therefore wall stress is high.

Studies *in vitro* have demonstrated that significant disruption of the pulmonary capillaries occurs at pressures of at least 80 mm Hg. One study demonstrates an *in vivo* threshold mean pulmonary artery pressure of around 80 to 95 mm Hg, above which significant hemorrhage is more likely to occur. On the basis of this theory, any factor or disease that increases pulmonary vascular pressures, such as hypervolemia, or increases the magnitude of the negative pressures in the lung during inspiration, such as dynamic upper airway obstruction, would be expected to increase the severity of EIPH. Neither experimentally induced laryngeal hemiplegia nor dorsal displacement of the soft palate increases pulmonary capillary transmural pressure. The limitation of the pulmonary capillary stress failure theory is that it does not in itself explain the site or pattern of progression of EIPH.

More recently a new theory for EIPH has been proposed based on locomotory forces. This theory claims to explain the site of initiation in the tips of the dorsocaudal lung, the nature of the damage, and the pattern of progression. The theory is based on the fact that during galloping, the absence of any bone attachment of the forelegs to the spine causes the shoulder to compress the cranial rib cage. The compression occurs largely during the stance phase when the limb is planted on the ground and the body swings over the limb. The shoulder is moved in a dorsal and cranial direction into the chest. The compression of the chest initiates a pressure wave of compression and expansion that spreads outward. However, because of the shape of the lung and reflections off the chest wall, the wave of expansion and compression becomes focused and amplified in the dorsocaudal lung. The alternate expansion and compression at the microscopic level in adjacent areas of lung tissue creates shear stress and capillary disruption. The notion that hemorrhage could occur in the lung in this way is consistent with the type of hemorrhage resulting from blunt trauma to the front of the chest or head, which commonly results in lung or brain damage; hemorrhage in car accident victims; and hemorrhage in boxers. In both accident victims and boxers the hemorrhage occurs at the opposite side of the body to that which is initially struck. The theory predicts that hemorrhage would be more severe on hard track surfaces. At present this theory has not been investigated.

The relationship between EIPH and airway inflammation is controversial. Two studies have shown that EIPH severity does not correlate with airway inflammation as judged by bronchoalveolar lavage cytology, airway obstruction, or airway reactivity. Furthermore, airway inflammation, not EIPH, is associated with reduced performance, leading to the notion that EIPH and lower airway inflammation are distinct entities. In contrast, recent surveys in Thoroughbred racehorses, using tracheal wash cytology as a measure of inflammation, showed an increased risk for EIPH with greater inflammation (unpublished data). The link between EIPH and inflammatory airway disease requires further study. In summary, a pragmatic view of EIPH may be that it is a multifactorial condition that involves airway, vascular, and locomotory components.



## EFFECTS OF EXERCISE-INDUCED PULMONARY HEMORRHAGE

Instillation of autologous blood into the airways causes inflammation and has been characterized by an early neutrophil influx. Although severe bleeding and visible epistaxis are probably now generally considered to affect performance, the effect of the "average" severity of bleeding is still unclear. Instillation of 200 ml of autologous blood (but not saline) into each lung decreases maximal oxygen uptake and by implication, would be expected to affect performance. However, how these acute experimental inoculations relate to natural EIPH is unknown.

## DIAGNOSIS

A definitive diagnosis of EIPH is provided by postexercise endoscopy and visualization of blood in the trachea. The classification of a horse as EIPH positive or negative has for the past 20 to 30 years been based primarily on the presence or absence of blood in the trachea after exercise. Simply recording EIPH as positive or negative is not particularly informative, especially if comparing a horse before and after treatment over time as the amount of blood may vary from as little as a single fleck to the trachea being completely covered with a film of blood. Various scoring systems have been described, for example the following:

*Grade 1:* flecks of blood

*Grade 2:* more than flecks, but less than a continuous stream

*Grade 3:* continuous stream less than half the tracheal width

*Grade 4:* continuous stream greater than half the tracheal width

*Grade 5:* airways awash with blood

The timing of endoscopic examination may be critical in cases of milder EIPH. If endoscopy is performed immediately postexercise, hemorrhage in the distal airways may not have progressed to the trachea. Similarly, if endoscopy is undertaken too long after exercise, blood may have been removed by the mucociliary escalator and swallowed. On the basis of most reports in the literature, endoscopy 30 to 60 minutes after exercise is recommended.

Relatively infrequently, blood in the trachea may not originate from the lung but from the upper airway and can be inhaled. In this instance the pattern is usually different to that seen in typical EIPH, with more blood seen in the proximal trachea and decreasing amounts of blood observed moving toward the carina.

The presence of free red blood cells and hemosiderophages in tracheal wash fluid indicates a previous episode of hemorrhage. In horses undertaking a canter or gallop this most likely suggests a history of EIPH. Although the numbers of free red blood cells are likely to be highest immediately after exercise, peak numbers of hemosiderophages may not be seen until 7 to 21 days after an episode of EIPH. It is difficult to relate numbers of hemosiderophages to the severity of a previous episode of EIPH.

More recently the concentration of red blood cells

(RBCs) in bronchoalveolar lavage (BAL) has been used to quantify EIPH. This is performed using an endoscope and has the advantage that a scoring of blood in the trachea and tracheal wash can be performed before BAL. The left and right lungs also can be selectively lavaged. BAL is performed around 30 to 60 minutes after exercise with a volume of 300 ml per lung, in one or two aliquots (i.e., 300 ml infused and aspirated or 150 ml infused, aspirated, and repeated). BAL may be performed conveniently without an endoscope, using a BAL tube (see Chapter 8.2: "Bronchoalveolar Lavage"). This has the advantage of sometimes allowing a better wedge to be obtained as a result of the balloon cuff, but the disadvantage of lacking the opportunity for direct visual inspection of blood and secretions in the airways.

The use of BAL allows better quantification of EIPH and detects EIPH at a level below that which results in visible blood in the trachea. Some reports say blood is seen in the trachea only when the sum of BAL RBC counts for the left and right lung exceed approximately 13,000 RBC/ $\mu$ l ( $13 \times 10^6$  RBC/ml) of BAL fluid. At this concentration of RBC, BAL fluid appears clearly red rather than simply orange tinged or pink.

In this author's laboratory sequential selective BAL in horses performed using an endoscope (as opposed to a blindly passed BAL tube) in both the left and right dorso-caudal lung has demonstrated that hemorrhage based on RBC counts is almost always greater in one lung than the other. No consistent side produces more hemorrhage between horses, but within a horse one side almost always shows more hemorrhage than the other.

Chest radiography appears to be of limited value in diagnosis of EIPH or even for detecting structural alterations in the lung as a result of many repeated episodes, even over a number of years. Pulmonary scintigraphy may detect moderate to severe alterations in the perfusion and possibly ventilation of the dorsocaudal lung. The use of radiolabeled red blood cells and scintigraphy to localize and or quantify hemorrhage is not useful because of general sequestration of labeled RBC by the lung, even in the absence of hemorrhage.

Ultrasound may be used to detect changes in the dorso-caudal lung fields associated with EIPH. The efficacy of this method to diagnose EIPH is unknown.

## TREATMENT

A variety of approaches are used to treat or manage EIPH. The precise etiology of EIPH is still far from clear and it may well be multifactorial or exacerbated by other coexisting disease processes or by inherited factors. However, to date the number of treatments shown under close scientific scrutiny in properly conducted trials to have any efficacy in terms of reduction of the severity of EIPH remains small. The goal of abolishing EIPH in an individual horse asked to exercise intensely is unrealistic. All horses have EIPH to some extent, even if only detectable on the basis of BAL or identification of hemosiderophages in tracheal wash (TW) or BAL. However, treatment to reduce a horse consistently experiencing EIPH at grade 4 or 5 to grade 2 to 3 may be achievable.

### Furosemide

The mainstay of treatment for EIPH for more than 25 years has been furosemide. In North America and some other racing jurisdictions, racing after furosemide treatment is permitted. However, in many other countries, whilst training horses on furosemide is permitted, its use during racing is banned. Now a wealth of evidence exists that furosemide reduces pulmonary vascular pressures both at rest and during exercise when administered in doses ranging from 250 to 500 mg 1 to 4 hours before exercise. Based on postrace surveys at racetracks furosemide does reduce the severity of bleeding (based on the amount of blood in trachea visualised endoscopically), but in a significant proportion of horses no clear reduction in EIPH occurs. The failure to record reductions in the severity of EIPH could point to a relative insensitivity of endoscopic grading in relation to the true severity of hemorrhage or to the fact that in some horses, the major underlying and precipitating cause of EIPH is not related to high pulmonary vascular pressures.

More recently a number of studies have been conducted using RBC counts in BAL to quantify the severity of EIPH in treadmill studies on horses treated with and without furosemide. The studies conducted in treadmill exercised horses showed that furosemide given intravenously (250 mg 30 min before or 500 mg given 4 hr before exercise) reduced RBC counts recovered in BAL fluid, and reduced pulmonary artery pressure to varying degrees. Given by nebulization or at the lower dose (250 mg) 4 hours before exercise, the effects were minimal in comparison. In general, furosemide had its greatest effect on horses that began with the most severe EIPH. These treadmill-based studies require replication in the field but show a clear link between pulmonary artery pressure, EIPH, and a dose-related effect of furosemide on the severity of EIPH.

### Other Vasodilators

Inhaled nitric oxide (NO; 80 ppm), a potent smooth muscle dilator, has been shown previously to decrease pulmonary vascular pressures during exercise in the horse. Infusion of nitroglycerine (an NO donor) at a dose of 20 µg/kg/min has been shown to decrease pulmonary vascular pressures at rest but to have no effect on pressures during maximal exercise and both control and treated horses show blood in the trachea after exercise. Oral nitroglycerine administered to horses at a dose of 22.5 mg, however, had no effect of pulmonary vascular pressures. The substrate for nitric oxide synthase (NOS), L-arginine at a dose of 200 mg/kg intravenously also has been reported not to reduce pulmonary vascular pressures during moderate intensity exercise. A more recent study has shown that inhaled NO (80 ppm) produced a small but consistent reduction in pulmonary vascular pressures, but in fact the RBC count in BAL was doubled with NO inhalation.

Although reduction in pulmonary vascular pressures by circulatory volume reduction with furosemide appears to be effective in reducing the severity of EIPH, reduction in pressure using vasoactive drugs may increase the severity of EIPH. This points to the fact that the precapillary arterioles may be constricted to protect the pulmonary capillaries and thus be the cause of the high pulmonary vascular

pressures seen in the horse. This would tend to suggest that treatment with vasodilators for EIPH is contraindicated.

### Nasal Strips

On the basis that a large proportion of the resistance to breathing occurs in the upper airways and particularly in the nasal passages, nasal dilator strips recently have been developed for horses (FLAIR, CNS Inc., Minneapolis, Minn.). The soft tissue overlying the nasal incisive notch is supported poorly and can be observed to be drawn inwards during inspiration, narrowing the nasal passages. This would have the effect of increasing inspiratory pleural (hence transmural) pressures, therefore placing greater stress on the blood vessels. Increased inspiratory pressures are a reflection of increased resistance to breathing. In fact, preliminary findings in one study have shown that the FLAIR strip decreases both upper airway resistance and inspiratory tracheal pressure in horses during treadmill exercise. In addition, the FLAIR strip also has been shown to decrease oxygen consumption during exercise, presumably as a result of decreased work of breathing. In essence, these studies demonstrate that nasal dilation devices have the potential to improve racing performance irrespective of EIPH.

In two recent treadmill studies, the FLAIR strip was shown to reduce the number of RBC in BAL by an average of 44% and by 74%. In the latter study, the greatest reduction in hemorrhage was seen in those horses exhibiting the higher volumes of bleeding in the control runs (no nasal strip). One recent study failed to demonstrate any change in the incidence of EIPH scored as blood present or absent in the trachea following exercise. Therefore, the effect on EIPH remains controversial. It is also important to emphasize that correct placement of a nasal strip is essential. The tendency for many users appears to be to place the strip too high on the nose. For this reason a template is included with the FLAIR strip to facilitate correct placement and should be used.

In the United Kingdom and many other racing jurisdictions the use of nasal strips currently is prohibited during racing but allowed during training. This is in contrast to North America where its use in racing is widespread. The efficacy demonstrated in the recent study (74% reduction in BAL RBC count) approaches that of furosemide on the same horses (80%). The FLAIR strip and furosemide in combination reduced the average BAL RBC count by 87%. Thus the use of nasal dilator strips based on these two treadmill studies, although on a limited number of horses, suggests that such devices merit strong consideration to use with or as an alternative to treatment with furosemide.

### Upper Airway Resistance

The efficacy of the nasal strip, which reduces upper airway resistance during high-intensity exercise, has stressed the potential importance of respiratory system resistance to EIPH. Resistance can be increased by a number of phenomena, including laryngeal hemiplegia, dorsal displacement of the soft palate, nasal, pharyngeal or tracheal collapse, guttural pouch disease, head flexion,

and pharyngeal inflammation. Thus all these sources should be examined during the investigation of EIPH in the individual horse.

### Miscellaneous Treatments

Phlebotomy has been used as a treatment in hypervolemic Standardbred trotters. A reduction of the total blood volume by 22% (36 ml/kg) decreased the severity of EIPH but treadmill performance and other indices of function, such as heart rate and oxygen uptake, were affected adversely.

Pentoxifylline, a phosphodiesterase inhibitor, is known to increase the deformability of RBCs, decrease blood viscosity, and potentially may decrease pulmonary vascular pressures during exercise and attenuate EIPH. Administration of 8.5 mg/kg pentoxifylline intravenously had no effect on pulmonary vascular pressures or the incidence of EIPH and did not enhance the effect of furosemide when given in combination.

Clenbuterol administered either alone or with furosemide apparently has no effect on pulmonary vascular pressures or pulmonary function in clinically healthy horses during exercise. Its effect on EIPH has not been investigated. Water restriction is not an uncommon practice in many countries that have racing, in the belief that the dehydration may alter "blood pressure" and thus prevent or reduce the severity of EIPH. To this author's knowledge, no information exists in the scientific literature that demonstrates any efficacy of water deprivation against

EIPH. Prolonged water deprivation and dehydration cannot be controlled in the same way as with diuretics such as furosemide, and any benefit from a reduction in severity of EIPH may be offset by a reduction in performance resulting from prolonged dehydration, electrolyte ( $\text{Ca}^{++}$ ,  $\text{K}^{+}$ ) depletion, and acid-base derangement.

Atrial fibrillation appears to increase the severity of EIPH in a few horses. Atrial fibrillation should therefore be ruled out in cases in which a sudden increase in the severity of EIPH occurs, possibly associated with loss of performance.

### Supplemental Readings

- Kindig CA, McDonough P, Fenton G et al: Efficacy of nasal strip and furosemide in mitigating EIPH in Thoroughbred horses. *J Appl Physiol* 2001; 91:1396-1400.
- Langsetmo I, Meyer TS, Erickson HH: Relationship of pulmonary arterial pressure to pulmonary hemorrhage in exercising horses. *Equine Vet J* 2000; 32:379-384.
- Oikawa M: Exercise-induced hemorrhagic lesions in the dorso-caudal extremities of the caudal lobes of the lungs of young Thoroughbred horses. *J Comp Pathol* 1999; 121:339-347.
- Pascoe JR, Jones JH: EIPH: the case for capillary stress failure. *Equine Vet J* 1994; 26:429-431.
- Schroter RC, Marlin DJ, Denny E: Exercise-induced pulmonary hemorrhage (EIPH) in horses results from locomotory impact induced trauma—a novel, unifying concept. *Equine Vet J* 1998; 30:186-192.

## CHAPTER 8.8

# Pneumothorax, Diaphragmatic Hernia, and Rib Fracture

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**T**rauma to the thorax can result in subtle clinical compromise or may manifest as a severe and life-threatening problem in a patient presented for hospitalization, critical care, or further assessment for possible surgical repair. If the injury has occurred in one of a group of pastured horses, no history of trauma to the thorax or abdomen may exist because the opportunity for observation is limited in such groups. Furthermore, the skin pigment and haircoat prevent the direct observation of bruising even in horses that are scrutinized closely.

The clinical signs of thoracic trauma range from stiffness or a stilted gait resulting from thoracic pain (pleuro-

dynia) to severe respiratory distress. Such distress usually can be discerned from that resulting from upper respiratory tract obstruction by the absence of upper respiratory stertor. However, thoracic auscultation is rarely useful in differentiation of trauma from pneumonia or bronchial disease. In classic cases of thoracic trauma, examination usually identifies the primary insult as extrapulmonary and causally related to the subsequent respiratory failure. However, it must be appreciated that abrupt abdominal compression also can cause pulmonary and diaphragmatic trauma, leading to pneumothorax and collapsed lungs, possibly with no external marks or signs of injury.

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## PNEUMOTHORAX

Pneumothorax occurs whenever air enters the pleural cavity and compromises the negative pressure that keeps the lungs expanded and allows the horse to breathe. Pneumothorax can be secondary to blunt trauma, penetrating wounds to the thorax from sharp objects, gunshot entry tracts, or barotrauma, or it may arise spontaneously. Open pneumothorax is a breach in the integrity of the thoracic wall, resulting in air influx and subsequent lung collapse. Closed pneumothorax is the leakage of air into the pleural space from a pulmonary source such as a bronchopleural fistula. Tension pneumothorax results from a tissue valve-like lesion that allows air to enter but not leave the pleural cavity. In all instances, air accumulates within the pleural space, leading to a loss of negative pleural pressure and possibly the development of positive pressure in the thorax. Spontaneous pneumothorax as described in humans has not been documented in horses. Therefore in the absence of coexisting lung disease presumably pneumothorax is due to trauma.

Penetrating wounds are usually obvious and may even be iatrogenic, for example in horses with indwelling thoracic tubes for the treatment of pleuropneumonia. In these cases, when fluid drainage from the tube wanes or ceases, the one-way valve at the end of the tube can become incompetent and allow air to be sucked into the pleural cavity. Rib fractures can be obvious when accompanied by external thorax wounds. However, they can be internal as a result of blunt trauma. The latter most commonly are observed as a result of birth trauma in neonates. In these cases a sharp rib fragment may lacerate a lung and allow for bronchopleural fistulation and subsequent lung collapse.

Hemothorax is the most commonly encountered consequence of lung laceration, and pneumothorax as a result of the injury is rare. Although rare, both pneumothorax and hemothorax may occur concurrently. Bronchopleural fistulas also may develop in association with gangrenous pneumonia or pleuropneumonia, but pneumothorax as a complication of this problem is relatively uncommon because the process of insidious necrosis promotes adherence or scarring to the thoracic wall.

The clinical compromise created by pneumothorax coincides with the collapse of one or both lungs secondary to the positive air pressure within the thoracic cavity. Pneumothorax may tend to be bilateral because horses commonly have an incomplete mediastinum. In cases of pleuropneumonia in which indwelling thoracic tubes have created a tension pneumothorax, pneumothorax is usually unilateral because the pleural effusion and inflamed mediastinum tend to prevent air movement between the pleural cavities.

### Clinical Signs

The clinical signs of pneumothorax include an acute increase in respiratory rate, sweating, cyanosis, and in profound cases of bilateral lung collapse, severe dyspnea. These clinical signs should provide for the primary suspicion of pneumothorax whenever an obvious thoracic wound, injury, or indwelling thoracic tube is present.

### Diagnosis

The diagnosis of pneumothorax secondary to thoracic trauma often can be made from the history but not by auscultation alone. Thoracic radiography can reveal a horizontal shadow beneath the thoracic transverse processes, which is consistent with a "line" representing a collapsed lung(s). Thoracic radiographs also can reveal primary lesions such as rib fractures or penetrating foreign bodies.

Ultrasonographic evaluation of the thorax reveals horizontal air artifacts in the midthoracic to dorsal regions, without the defining pattern of the pleura. In these cases, although the parallel lines of air reverberation artifact is present as is the case in horses with normal lungs, the examiner is not able to identify the sliding motion of the visceral pleura against the parietal pleura as is apparent in a normal examination. This finding, in conjunction with the clinical examination, should be considered pathognomonic for pneumothorax and is an indication for suction as an immediate treatment for the respiratory distress.

When neither radiography nor ultrasonography is available, the clinician should not hesitate to use suction as a means of diagnosis. The relief provided by treatment should be considered consistent with the diagnosis of pneumothorax.

### Treatment

The preferred treatment is the prompt removal of the free air by suction of the dorsal reaches of the thorax. This procedure rapidly reexpands the lung and relieves respiratory distress. In horses with an open thoracic wound, surgical closure of the wound is necessary regardless of whether the pneumothorax is unilateral or bilateral. If both lungs are collapsed, surgical closure may require intubation under anesthesia and positive pressure ventilation during the thoracic repair. When an indwelling thoracic tube is the cause of the pneumothorax, the tube should be clamped and the Heimlich valve or condom replaced.

Thoracic cavity air suction is performed in patients with a competent external thorax by surgically preparing a penetration site in the upper midthorax between the ribs. The site is anesthetized locally followed by a stab incision made full thickness through the skin using a number-15 scalpel blade. Next a 4-inch blunt teat cannula with an optional three-way stopcock is inserted into the incision and advanced through the intercostal musculature until the popping sensation denoting penetration into the pleural cavity is appreciated. If a suction apparatus is available, the cannula is attached to vacuum tubing and a vacuum is applied. If a suction machine is not available, air can be repeatedly aspirated by use of a 60-ml syringe. The lung should be reinflated sufficiently to begin rubbing or causing friction against the tip of the teat cannula. Ultrasound can be used to detect the return of the sliding visceral pleura once reinflation has occurred. The cannula is then removed and a single interrupted suture is placed aseptically in the skin for closure of the incision site. The patient should show an obvious decrease in respiratory effort and dissipation of respiratory distress. Thoracic radiographs can be obtained to further document the expansion of the lung, but in most cases, ultrasound imaging

along with the patient's relief, are sufficient to document the success of the procedure.

## DIAPHRAGMATIC HERNIA

Diaphragmatic hernia in horses is uncommon but not rare. Most referral practices are presented with one or more cases annually. The causes are associated principally with trauma to either the thorax or abdomen, but the injury also can occur after exertion such as that experienced by stallions during breeding. Congenital diaphragmatic hernia can occur in neonates when closure of the crura does not occur. Blunt trauma such as falls, kicks, or collisions can result in tearing or rupture of the diaphragm.

Diaphragmatic hernia also can occur without an obvious cause and may precipitate signs of colic, mild to moderate elevations in respiratory rate, or toxic shock secondary to bowel incarceration or strangulation. The size of the tear within the diaphragm is an important determinant of the clinical signs manifested, in that chronic tears may go unnoticed by clients until such time as the abdominal viscera dislocate into the thorax and become compromised. Acute tears in the diaphragm may be associated with hemorrhage into both the abdominal and thoracic cavities. Fractures of the ribs in the caudal thorax have resulted in the "sawing" or incising of sharp bone edges at the fracture site through adjacent diaphragmatic musculature, creating a discontinuity in the sheetlike muscular surface through which abdominal structures evertate.

### Clinical Signs

Clinical signs of a diaphragmatic hernia may include a moderate to severe increase in respiratory rate, concurrent hemorrhagic shock, colic, and endotoxic shock. If the horse has colic, a rectal examination may suggest a relative absence of normal abdominal viscera. Auscultation may reveal absence of breath sounds in the ventral thorax, and thoracic percussion can define similar areas of decreased aeration. Some horses with diaphragmatic hernias can show relatively few clinical signs, because little pulmonary or bowel compromise occurs. Occasionally, diaphragmatic hernias are discovered incidentally at *post mortem*, supporting the notion that they can be benign in horses not subjected to heavy exertion.

### Diagnosis

The diagnosis of a diaphragmatic hernia is based largely on a clinical suspicion often confirmed during an exploratory celiotomy of a horse that presents with signs of colic. Before surgery, suspicions of a diaphragmatic hernia can be confirmed by thoracic radiography or ultrasonographic examination. Thoracic radiographs can reveal obliteration of the ventral views of the heart and posterior vena cava and the presence of lines that represent gas-filled loops of bowel within the thorax. The use of ultrasound can demonstrate abdominal viscera in direct contact with the lungs or heart, without obscuring the latter structures from view. During ultrasound examination

of the thorax the clinician may observe aberrant structures filled with fluid and/or gas, or may observe peristaltic movements of bowel within the thorax. If the patient presents with signs of colic, the peritoneal fluid obtained from abdominal paracentesis does not consistently reflect bowel compromise because abnormal fluid may be confined to the thoracic cavity.

### Treatment

Treatment of diaphragmatic hernia depends on the degree of clinical compromise. Some horses with a chronic hernia show few clinical signs. In these cases, treatment is optional and, if elected, involves surgical repair. Surgical correction can be complicated by the need for concurrent repair of fractured ribs or treatment of intestinal compromise. The herniated bowel must be returned to the abdomen and strangulating or obstructing lesions of either small or large intestine must be corrected. Surgical repair of the diaphragm often requires the use of surgical "mesh" to obliterate the hernia because primary closure of the muscular diaphragm is usually not a feasible option. Postoperative care includes medical management of any associated clinical disorders and stall confinement until the hernia repairs. In horses that show an immediate response to treatment, the prognosis is relatively favorable.

## FRACTURED RIBS

Fractured ribs most commonly are observed in neonates in conjunction with birth trauma. Rib fractures in older individuals most often result from collisions or kicks or falls. Birth trauma is the most common cause of rib fracture, and most neonates with fractures do not require medical or surgical intervention. However, rib fracture can cause life-threatening compromise to the integrity of the cardiopulmonary system and diaphragmatic hernia. Death can be due to hemorrhage into the thorax, pericardium, or abdomen, or shock, or a traumatic contact of the rib with the epicardium or myocardium that causes cardiac arrest.

### Clinical Signs

The clinical signs of fractured ribs are variable. Crepitus cannot be palpated consistently over the damaged area of the thoracic wall. In foals, simultaneous observation and palpation of the thoracic cage may reveal asymmetry of the thorax, especially at or near the costochondral junctions. Crepitation or "clicking" over a rib, heard with or without a stethoscope, is pathognomonic for the injury. Some patients reveal moderate thoracic edema ventral to the fracture sites. A stilted gait can indicate thoracic pain or the patient may "grunt" when manipulated or maneuvered. In severe cases, involving fractures in multiple consecutive ribs, the patient is in respiratory distress and presents with a flail thorax. The latter can be recognized when inspiratory effort results in collapse of the thoracic wall inward rather than the expected normal outward movement. If the patient has simultaneous pallor of the mucous membranes, internal hemorrhage should be

suspected and promptly pursued in the diagnostic evaluation. Internal hemorrhage, including hemothorax, hemopericardium, and abdominal hemorrhage, may indicate that the diaphragm has been lacerated. Pneumothorax is an uncommon finding with fractured ribs in neonates but may be more likely in older individuals with fractures secondary to blunt trauma.

The location of the rib fractures is an important determinant of prognosis. Fractures in the cranioventral portion of the thorax, in proximity to the heart, can cause cardiac laceration and sudden death. Midthoracic rib fractures more frequently cause pulmonary laceration and hemothorax, occasionally with pneumothorax. Fractures in the mid-to-caudal thorax are capable of lacerating the diaphragm and causing secondary lung or abdominal visceral lesions.

### Diagnosis

The diagnosis of fractured ribs may be obvious when palpable crepitus is associated with an underlying rib. Ancillary diagnostic procedures include ultrasound evaluation and thoracic radiography. In most cases, use of ultrasound can reveal both rib fracture and displacement. Ultrasound is better than radiography for detecting the site of injury and also detects hemothorax, hemopericardium, pneumothorax, or diaphragmatic hernia. A single radiographic view provides an overall assessment of the thorax but ultrasound provides a detailed map.

### Treatment

The treatment of choice for fractured ribs is rest and confinement for 1 to 3 weeks. This conservative treatment is successful in nearly all cases of uncomplicated rib fracture. Supportive care is indicated for foals in pain, and manual assistance in helping foals to rise and nurse should be pro-

vided in a manner that avoids direct compression of either the fracture sites or the sternum. Affected foals may be assisted safely by lifting them from sternal recumbency by the elbows. Sedation may be required to prevent flailing or harmful struggling of some patients, and oxygen supplementation via nasal insufflation is indicated for obvious hypoxemia. If severe hypoxemia is present concurrently with a flail thorax, longer-term phenobarbital sedation may be required to maintain the foal in lateral recumbency. In these cases, the intact thoracic wall should be uppermost and occasionally the foal should be allowed to rest on its sternum. Foals that turn over can compress the underlying damaged lung. If the patient is allowed to be ambulatory, the primary concern is cardiac laceration and arrest if cranioventral fractures are further displaced by overactivity.

Surgical treatment of rib fractures is uncommon, but in these authors' practice stabilization has been provided by use of dynamic compression plates. The long-term outcome of this procedure currently is being investigated. In cases where rib fractures are responsible for diaphragmatic hernia, surgical repair is essential to a favorable prognosis.

### Supplemental Readings

- Beech J: *Equine Respiratory Disorders*, Philadelphia, Lea & Febiger, 1991.
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- Sprayberry KA, Bain FT, Seahorn TL et al: 56 Cases of rib fractures in neonatal foals hospitalized in a referral center intensive care unit from 1997-2001. *Proceedings of the 47th Annual Meeting of the American Association of Equine Practitioners*, pp 395-399, 2001.

## CHAPTER 8.9

# Aerosolized Drug Delivery Devices

BONNIE R. RUSH  
*Manhattan, Kansas*

**A**erosolized drug therapy has been the standard treatment approach in human medicine for patients with noninfectious respiratory disease for 20 years. Administration via inhalation improves drug safety and efficacy by reducing the total therapeutic dose, minimizing drug exposure to other body systems, and allowing

direct delivery of the drug to the lower respiratory tract. In most instances, the response to aerosolized drug administration is more rapid than to systemic drug administration. The equine patient is an ideal candidate for inhalation therapy for several reasons: a highly cooperative nature, obligate nasal breathing, rostrally placed and large

suspected and promptly pursued in the diagnostic evaluation. Internal hemorrhage, including hemothorax, hemopericardium, and abdominal hemorrhage, may indicate that the diaphragm has been lacerated. Pneumothorax is an uncommon finding with fractured ribs in neonates but may be more likely in older individuals with fractures secondary to blunt trauma.

The location of the rib fractures is an important determinant of prognosis. Fractures in the cranioventral portion of the thorax, in proximity to the heart, can cause cardiac laceration and sudden death. Midthoracic rib fractures more frequently cause pulmonary laceration and hemothorax, occasionally with pneumothorax. Fractures in the mid-to-caudal thorax are capable of lacerating the diaphragm and causing secondary lung or abdominal visceral lesions.

### Diagnosis

The diagnosis of fractured ribs may be obvious when palpable crepitus is associated with an underlying rib. Ancillary diagnostic procedures include ultrasound evaluation and thoracic radiography. In most cases, use of ultrasound can reveal both rib fracture and displacement. Ultrasound is better than radiography for detecting the site of injury and also detects hemothorax, hemopericardium, pneumothorax, or diaphragmatic hernia. A single radiographic view provides an overall assessment of the thorax but ultrasound provides a detailed map.

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direct delivery of the drug to the lower respiratory tract. In most instances, the response to aerosolized drug administration is more rapid than to systemic drug administration. The equine patient is an ideal candidate for inhalation therapy for several reasons: a highly cooperative nature, obligate nasal breathing, rostrally placed and large



nares, slow breathing rate and inspiratory flows, and a spectrum of diseases amenable to topical treatment.

However, initially devices such as nebulizers designed for delivery of aerosolized drugs to the lower respiratory tract of horses were cumbersome, expensive, and marginally efficacious. Today, efficient systems for drug delivery are being developed rapidly and inhalation therapy has become increasingly popular for treatment of lower respiratory tract disease. The most important aspects of aerosol administration for horses are efficient pulmonary drug delivery and ease of administration. The disadvantages of the aerosol route of administration include inability to access obstructed airways, high start-up costs, frequency of drug administration, potential for direct airway irritation by some aerosol preparations, respiratory contamination with environmental microorganisms, and contributions to air pollution from propellants. To date, inhalation therapy for horses has focused predominantly on administration of bronchodilating agents and corticosteroid preparations for treatment of recurrent airway obstruction (heaves). Aerosolized antimicrobial agents are under investigation for treatment of bacterial infection of the lower respiratory tract in horses. Bioactive proteins (insulin, antithrombin III, growth hormone) and hormones in aerosol currently being studied in humans may have future application in the horse.

Aerosols are defined as a gas containing finely dispersed solid or liquid suspended particles. The primary determinants of the efficiency of pulmonary deposition of an aerosol preparation include size, shape, viscosity, density, and hygroscopic growth of particles. Most therapeutic aerosols are heterogeneous (heterodispersed), and their aerodynamic behavior is described best by the mass median aerodynamic diameter (MMAD). Aerosol preparations with an MMAD of 1 to 5 microns produce the best therapeutic results in humans and are the target particle size for inhalation therapy in horses. These small particles penetrate deep within the respiratory tract, and particles less than 2 microns can penetrate alveoli. The cross-sectional area ( $\text{cm}^2$ ) of the lung increases dramatically at the level of the respiratory zone; therefore the velocity of gas flow during inspiration rapidly decreases at this level. Because the velocity of gas falls rapidly in the region of the terminal bronchioles, small particles sediment out in these airways. Moderate-size particles (5 to 10 microns) frequently settle out by sedimentation in larger more central airways (trachea, bronchi). Large aerosolized particles (>10 microns) affect the upper respiratory tract via inertial impaction. The majority (90%) of particles below the target size (<0.5 microns) are inhaled and exhaled freely and rarely affect the respiratory tract.

In addition to particle size, the patient's tidal volume, inhalation and exhalation flow rates, and upper respiratory tract anatomy affect pulmonary drug deposition. Because these physiologic factors, in particular nasal breathing, affect pulmonary drug deposition, equine clinicians cannot extrapolate data generated from human subjects regarding specific drugs or devices to equine patients. Finally, all aerosolized solutions should be isotonic with neutral pH and should not contain chemical irritants such as benzalkonium, ethylenediaminetetraacetic acid (EDTA), chlorbutol, edetic acid, and metabisulfite.

## METERED-DOSE INHALANT SYSTEMS

Several devices have been designed for convenient administration of aerosolized drugs formulated in a metered-dose inhaler (MDI) canister to horses with recurrent airway obstruction (Figure 8.9-1). The advantages of an MDI system include rapid administration, consistent ex-valve dose delivery, minimal risk of pulmonary contamination with environmental microorganisms, ease of cleaning/maintaining equipment, wide availability, and no requirement for electricity. Pulmonary drug delivery in human patients using MDI devices varies with the specific device, drug preparation, and patient technique. Ideally, the MDI is actuated in early inhalation, during a slow (5-second) breath, followed by a 10-second period of breath holding to allow particles to deposit in the lower airway. These conditions are met only in humans. The equine patient inhales over 2 to 3 seconds with no breath hold so that lung deposition is lower.

Chlorofluorocarbon (CFC) propellant has been an essential component of MDI drug delivery systems. However, CFCs were recognized to have a depleting effect on the ozone layer in 1985. One CFC molecule is capable of destroying 100,000 molecules of stratospheric ozone and CFC molecules persist in the atmosphere for centuries. Propellants containing CFCs are being phased out of most applications, and newly developed inhalant products are formulated with CFC-free, ozone-friendly solution propellants. Hydrofluoroalkane-134a (HFA) is an inert, non-toxic replacement propellant for CFCs. It is eliminated from the body by ventilation, without evidence of accumulation or metabolism. Because HFA formulations are dissolved in solution, rather than held in suspension, shaking is not necessary between actuations allowing immediate administration of drug with each breath.

The efficacy of HFA formulation of some drugs (salbutamol, fenoterol, ipratropium) is equivalent or greater than the CFC preparations. The HFA formulations of beclomethasone, for example, produce a greater total mass of fine drug particles, which improves pulmonary drug deposition and reduces the required daily dose substantially. A twofold to tenfold improvement occurs in pulmonary drug delivery of beclomethasone using an HFA formulation over a CFC formulation depending on the delivery device. Less actuated drug is deposited in the pharynx using an HFA propellant, which reduces the incidence of local and systemic side effects. Because of the greater uniformity of fine particle size, the HFA formulations reduce the need for a spacer in the drug delivery device because spacers are used to enhance fine particles by exclusion of larger particles.

The Equine AeroMask (Trudell Medical International, London, Ontario) is the most versatile of the delivery systems because it can be used for administration of aerosolized drugs via MDI devices, nebulization solution, or dry powder inhaler (see Figure 8.9-1, A). This system allows the clinician to administer any drug that is available for human asthma therapy to horses with heaves. Drug is actuated or nebulized into a spacer device designed with a one-way inspiratory valve. The mask must fit snugly around the muzzle to ensure adequate negative inspiratory pressure to facilitate drug delivery. Based on radiolabeling studies, drug delivery to the lower respiratory tract



**Figure 8.9-1** Metered-dose inhalant delivery devices for horses. **A**, Equine AeroMask fits over the entire muzzle and is equipped with a spacer device (AeroChamber attachment) for use with any metered-dose inhaler available for human inhalant administration. Attachments for nebulization of liquid medication and dry powder inhalant delivery are available, but not shown. **B**, Equine Aerosol Drug Delivery System fits snugly within the left nostril, is preloaded with one canister of specified drug, and is disposable when the entire canister has been actuated. **C**, The Equine Haler device fits over the left nostril of the horse and is recommended for use with any metered-dose inhaler designed for human inhalant administration.

through the use of the Equine AeroMask with an MDI is approximately 6% of actuated drug when a CFC propellant is used and approximately 14% of actuated drug when an HFA propellant is used. The large portion of the drug that does not reach the lung is either retained in the spacer or trapped on the surface of the external nares. Drug is distributed uniformly throughout all pulmonary fields.

The Equine Aerosol Drug Delivery System (EADDs, developed by 3M Animal Care Products) is a novel, handheld device designed for administration of aerosolized drugs in horses (see Figure 8.9-1, B). The EADDs fits snugly into the left nostril of the horse and therefore

avoids a large wastage of drug on the external nares. The operator actuates a puff at the onset of inhalation, denoted by a flow indicator within the device. The operator must pay close attention to the timing of drug delivery, because drug delivered during mid- to late inhalation may reach the tracheal lumen only to be exhaled. The advantage of the EADDs is efficiency of drug delivery. The mean MMAD generated using this system with a CFC propellant is  $2.3 \pm 2$  microns, and approximately 23% of actuated drug is delivered to the lower respiratory tract. The mean MMAD using an HFA propellant is 1.1 microns, and approximately 43% of actuated drug is delivered to the lower respiratory tract in horses.

Ventilation imaging using radiolabeled aerosol confirms that drug is deposited in all pulmonary fields with minimal deposition in the nasal cavity, oral pharynx, or trachea. Currently, the EADDs is approved and commercially available only for administration of albuterol sulfate in an HFA propellant (Torpex, Boehringer-Ingelheim Vetmedica, Inc., St. Joseph, Mo.). The device was not designed for administration of interchangeable drugs using human MDIs. Rather, the device is distributed with a preloaded canister of albuterol sulfate and is designed for disposal after the drug has been dispensed.

The Equine Haler (Equine Healthcare APS, Hillerød, Denmark) is a spacer device that fits over the entire left nostril of the horse and is designed for administration of aerosolized drug using any human MDI device (see Figure 8.9-1, C). The mean particle size generated using the Equine Haler is 2.1 microns with a range of 1.1 to 4.7  $\mu\text{m}$  (fluticasone/CFC-free propellant). Drug deposition in the lower respiratory tract was reported to be  $8.2 \pm 5.2\%$  of the actuated dose with diffuse pulmonary drug delivery that is adequately distributed to the periphery of the lung. As for the AeroMask, nasal trapping and retention in the spacer contributed to drug wastage. Unlike the AeroMask, the Equine Haler can accommodate any size horse without difficulty in creating an airtight seal over the muzzle. Poor pulmonary drug delivery can occur if the administrator does not pay particular attention to align the MDI with the spacer and the spacer apparatus with the nasal passages of the horse during actuation. In all cases, the reaction of the horse to the release of the aerosol, by jerking of the head, or alteration of breathing pattern can detract for lung delivery.

In summary, the EADDs system delivers a much greater proportion of drug to the lung but must be inserted into the nostril. The AeroMask and Equine Haler are less efficient because of drug trapping on the nares but have the advantage of being less invasive, and both incorporate spacer-valve combinations that reduce asynchrony of actuation with inspiration and do a better job of selecting fine particles, an important consideration when employing fine CFC-based MDIs.

## MECHANICAL NEBULIZERS

Ultrasonic nebulizers and jet nebulizers are ozone-friendly delivery systems, used as alternatives to MDI. Ultrasonic nebulizers produce aerosol particles using vibrations of a quartz (piezo-electric) crystal, and particle size is inversely proportional to the operating frequency. High quality ultrasonic nebulizers are required to produce satisfactory particle size. Jet (pneumatic) nebulizers operate by the Venturi effect (dry air compressor) to fragment therapeutic solutions into aerosol particles.

The diameter of particles generated by a jet nebulizer is inversely proportional to the airflow, and minimum gas flow rates of 6 to 8 L/min are required to generate suitable particle diameter ( $<5 \mu\text{m}$ ) for pulmonary delivery. Jet nebulizers are readily accessible, inexpensive, and easy to use. The primary disadvantage of jet nebulization is noise generated by the system. Ultrasonic nebulizers are silent; however, they are expensive and fragile. High pressure jet nebulization (Hudson RCI, Temecula, Calif.) using a de-

livery system developed for horses (Nebul, Agritronix Int, Meux, Belgium) delivers approximately 7% of the drug to the pulmonary system, and ultrasonic nebulization (Ultra-Neb, DeVilbiss, Somerset, N.J.) delivers approximately 5% of the drug to the pulmonary system. Deposition of radiolabeled drug into peripheral pulmonary fields using jet nebulization is superior to ultrasonic nebulization. Pulmonary contamination with environmental bacteria and fungi may occur using these aerosol delivery systems; therefore rigorous disinfection of the equipment is required to avoid this complication. Aerosol therapy via jet and ultrasonic nebulization requires an administration time of approximately 10 to 20 minutes, versus less than 2 minutes for many MDI drug dosages.

## DRY POWDER INHALANT (DPI) DEVICES

Dry powder inhalant devices offer several advantages over nebulization systems, including rapid drug administration, minimal risk of environmental contamination with drug, and no requirement for electricity. The DPIs comprise numerous capsules containing a single dose of drug and a rotor. The rotor of the DPI device is breath-actuated, and the device punctures gelatin capsules containing powdered drug and releases it into a chamber for inhalation by the patient. This system eliminates the need for the operator to synchronize administration with inhalation. The entire dose from an individual dry powder capsule is delivered during a single inhalation; prolonged duration of inspiration and multiple inhalations do not improve pulmonary drug delivery.

DPI devices are designed for use by human patients, but have been adapted for drug administration to horses using a specialized facemask (EquiPoudre, Agritronics Int) or a unique adaptor to the Equine AeroMask. The efficiency of drug delivery can be influenced by relative air humidity, airflow, and position. The masks used with DPIs must fit snugly around the muzzle to create adequate inspiratory pressure and flow rates by the horse to ensure sufficient inhalant emptying rates. The minimum flow rate necessary to trigger the device (60 L/min) is generated easily by healthy and heaves-affected horses. The DPI device and mask must be aligned with the longitudinal axis of the nasal cavities to avoid affecting the powder within the mask or nasal passages.

High relative humidity increases retention of drug within the device because of aggregation of powder. If the relative air humidity exceeds 95%, water actually penetrates the DPI and significantly limits drug delivery. Manufacturers recommend administration of DPIs under conditions of low relative humidity to minimize the loss of powder within the device. Ipratropium bromide is the most extensively investigated DPI preparation for administration to horses and has demonstrated effective bronchodilation in heaves-affected horses.

Numerous devices may be used to deliver aerosolized antiinflammatory and bronchodilator drugs into the equine lung. The equine clinician should be familiar with the technical aspects of aerosolized drug administration because the appropriate drug dosage and frequency of administration for inhalation therapy varies depending on the efficacy of the drug, drug formulation, severity of disease, and efficiency of

the delivery device. The quality and quantity of pulmonary drug deposition vary most among the commercially available mechanical nebulizers. The clinician must select a high-quality ultrasonic or jet nebulizer to ensure pulmonary drug delivery. The metered-dose inhalant systems produce the most consistent drug delivery given appropriately fitted equipment. Each system has advantages and disadvantages that must be taken into consideration relative to the size, cooperativity, and preferences of the horse and owner.

### Supplemental Readings

- Duvivier DH, Votion D, Vandenput S et al: Review: aerosol therapy in the equine species. *Vet J* 1997; 154:189-202.
- Hoffman A: Inhaled medications and bronchodilator use in the horse. *Vet Clin North Am Equine Pract* 1997; 13(3):519-530.
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## CHAPTER 8.10

# Use of Aerosolized Bronchodilators and Corticosteroids

MELISSA R. MAZAN

*North Grafton, Massachusetts*

In recent years, aerosolized drug therapy in the horse has transitioned from a curiosity to a well established treatment modality. Practitioners and owners alike have recognized the benefit of topical application of bronchodilator and glucocorticoid drugs, thus avoiding the side effects and even toxicities associated with the systemic delivery of these drugs. Although several publications regarding aerosolized drug therapy in the horse have been published in the past 5 years, a dearth of information concerning efficacy, pharmacokinetics, and pharmacodynamics of aerosolized drugs in the horse exists. Often, treatment rests upon extrapolation from discoveries made in the treatment of human asthma or chronic obstructive pulmonary disease (COPD) to the horse. Further complicating the matter is the confusion that still exists concerning various manifestations of inflammatory, non-septic lower respiratory disease in horses. For the purposes of this discussion, this author will adhere to the recommendations of the recent international workshop on equine chronic airway disease, which recognized two distinct entities: recurrent airway obstruction (RAO, "heaves") and inflammatory airway disease (IAD). Heaves is a familiar disease, whereas IAD is less well defined but encompasses the signs of cough, exercise intolerance, mucus in the airways, and varying degrees of lower airway inflammation in younger horses (see Chapter 8.3: "Inflammatory Airway Diseases: Definitions and Diagnosis in the Performance Horse"). Most practitioners agree that these are two very different clinical entities that clearly demand different treatment recommendations. Nonetheless, it is now generally recognized that inflammation is of vital sig-

nificance in both conditions. Antiinflammatory treatment is therefore the cornerstone of therapy for each.

### TREATMENT STRATEGY

The goals of treatment must be clear in order for client, patient, and veterinarian satisfaction, which entails a team approach and acceptance that treatment may be a lifelong issue that may be modified but is unlikely to disappear. Goals in treating RAO should include: (1) immediate relief of the bronchospasm that causes dyspnea, (2) reduction of lower airway inflammation that causes cough and mucus hypersecretion, (3) long-term prevention of episodes of heaves by control of lower airway inflammation and airway obstruction, and (4) return to limited or even full athletic potential. The goals for treatment of nonseptic IAD are similar, as follows:

1. Eliminate bronchoconstriction that impairs performance.
2. Reduce mucus production and airway plugging.
3. Reduce coughing.
4. Reduce airway reactivity.
5. Prevent recurrences.

Aerosol therapy has its place in each of these goals, although systemic corticosteroids are usually necessary for initial reduction of airway inflammation, and environmental control is paramount in long-term control of recurrent airway obstruction (RAO; see Chapter 8.4: "Heaves [Recurrent Airway Obstruction]: Practical Management of Acute Episodes and Prevention of Exacerbations"). To achieve success, the

the delivery device. The quality and quantity of pulmonary drug deposition vary most among the commercially available mechanical nebulizers. The clinician must select a high-quality ultrasonic or jet nebulizer to ensure pulmonary drug delivery. The metered-dose inhalant systems produce the most consistent drug delivery given appropriately fitted equipment. Each system has advantages and disadvantages that must be taken into consideration relative to the size, cooperativity, and preferences of the horse and owner.

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veterinarian and client must plan for regular check-ups and be prepared for changes in treatment strategy that might be necessary. Owner education is critical in achieving compliance. Establishing a reasonable definition of "return to athletic use" is critical to client satisfaction. Looking forward to returning a mildly affected, young racehorse to full racing potential is reasonable, whereas a reasonable goal for a horse with RAO might be a much more modest return to light pleasure riding. When available, lung function testing before and after administration of a bronchodilator can be very useful for identifying the horse that is less likely to respond to conventional therapy. Horses with poor initial responses to either bronchodilators or steroids may not respond as readily in the long term. Horses with IAD that exhibit intense airway hyperreactivity or high numbers of inflammatory cells also may be less responsive to therapy.

### MONITORING RESPONSE TO THERAPY

It is important to have a baseline assessment of the horse before initiating therapy. Ideally, this includes careful physical examination, auscultation with and without a re-breathing bag, observation during exercise, baseline pulmonary function testing and measure of airway reactivity (IAD), or, in the case of horses with RAO, the effect of bronchodilation. Bronchoalveolar lavage cytology should

be evaluated in either case. Although pulmonary function testing is currently available only at a few specialized veterinary clinics, user-friendly systems for field-testing may become available, thus making objective baseline assessments available to practitioners. A clinical scoring system has been devised; however, it does not discriminate IAD from normal sufficiently for clinical use. Horses with heaves can be scored on abdominal lift (normal, mild, moderate, severe increase: 1-4) and nasal flaring (normal, mild, moderate, severe increase: 1-4). The goal of a thorough baseline assessment is to facilitate a treatment regimen tailored to the individual horse and to monitor response to therapy. This author offers free lung function testing one month after initiation of therapy to assess response and fine-tune therapy for the upcoming months. Communication with owners and referring veterinarians is encouraged to facilitate this process.

### TREATMENT MODALITIES

Aerosolized drugs can be used to provide both quick relief of respiratory difficulty and long-term treatment (Table 8.10-1). Quick relief can be provided by short-acting  $\beta_2$ -adrenergic agonists or anticholinergic drugs. Long-term therapy is provided by use of antiinflammatory drugs and perhaps long-acting  $\beta_2$ -adrenoceptor agonists.

**Table 8.10-1**  
**Recommended Dosages for Aerosolized Medications in Horses**

Class	Active Ingredient	Formulation	Dosage	Manufacturer/ Brand Name	Frequency
Corticosteroids	fluticasone propionate	44, 110, or 220 $\mu$ g/puff	2200 $\mu$ g	Glaxo Wellcome/ Flovent 220	Once to twice daily
	beclomethasone dipropionate	HFA 40-80 $\mu$ g/puff	500-1500 $\mu$ g	3M Pharmaceuticals/ QVAR	Once to twice daily
		CFC 42-84 $\mu$ g/puff	1500 $\mu$ g	Glaxo Wellcome/ Beclovent	Once to twice daily
Short-acting $\beta_2$ -agonists	albuterol (Salbutamol)	90 $\mu$ g/puff	450-900 $\mu$ g	Schering Corporation/ Proventil	prn; not to exceed 4 $\times$ /week unless in conjunction with corticosteroid
	fenoterol	0.1 mg/puff	1-3 mg	Boehringer Ingelheim/ Berotec	prn; not to exceed 4 $\times$ /week unless in conjunction with corticosteroid
Long-acting $\beta_2$ -agonists	salmeterol	25 $\mu$ g	210 $\mu$ g	Glaxo Wellcome/ Serevent	Once to twice daily <i>in conjunction with corticosteroid therapy</i>
Mast cell stabilizers	sodium cromoglycate	800 $\mu$ g	8-12 mg	Aventis Pharmaceuticals/ Intal	Once to twice daily
	nedocromil sodium	1.75 mg	17.5 mg	Aventis Pharmaceuticals/ Tilade	Once to twice daily
Parasympatholytics	ipratropium bromide	20 $\mu$ g	90-180 $\mu$ g	3M Pharmaceuticals/ Atrovent	2-4 $\times$ daily

prn, As needed.

## Short-Acting Bronchodilator Drugs

### *$\beta_2$ -Adrenoceptor Agonists*

Short-acting  $\beta_2$ -adrenoceptor agonists such as albuterol and fenoterol are vitally important in treatment of acute exacerbations of RAO. The horse that is laboring to breathe and has paroxysmal coughing will experience rapid relief with the use of  $\beta_2$ -agonists. However, these are correctly termed *rescue drugs* and should not be used on a regular basis. Remembering that the inflammatory condition will persist despite apparent improvement because of transient bronchodilation and that the disease may worsen if other therapy is not administered concurrently is important. Regular use of  $\beta_2$ -agonists in the absence of antiinflammatory medication may mask clinical signs that would otherwise indicate progressive worsening of the disease—in particular, further airway obstruction with mucus.

Short-acting  $\beta_2$ -agonists are not performance-enhancing in humans, and increasing evidence supports this finding in horses. Nonetheless, albuterol and similar drugs remain proscribed by all equine sporting events, and due care should be taken to stop drug administration before competition. Short-acting  $\beta_2$ -agonists can be useful in horses with IAD and underlying airway obstruction to improve the return to training. Administration of albuterol may also increase the peripheral lung deposition of other concurrently used drugs such as corticosteroids. Short-acting bronchodilators are also useful during lung function testing to assess the reversibility of airway obstruction in horses with RAO. Most horses bronchodilate in response to 450  $\mu\text{g}$  of albuterol, irrespective of the delivery device (see Chapter 8.9: “Aerosolized Drug Delivery Devices”).

Although aerosolized  $\beta_2$ -agonists have a relatively low incidence of side effects, excessive use, or even standard use in sensitive individuals may result in systemic effects such as trembling, anxiety, and cardiac arrhythmias. This author has noted these signs in individuals treated with 900  $\mu\text{g}$  of albuterol, whereas other individuals tolerate a higher dose. Repeated use of the drug tends to decrease side effects as the body down-regulates receptors. Very occasionally, horses may exhibit signs of bronchoconstriction with  $\beta_2$ -agonists. This paradoxical response is transient—probably caused by the effects of the drug vehicle on airways.

### *Anticholinergic Drugs*

In horses, bronchoconstriction is vagally mediated; thus parasympatholytic drugs are effective in mitigating bronchospasm. Ipratropium bromide is a quaternary derivative of atropine, and this formulation results in little systemic uptake. It antagonizes the acetylcholine receptor on bronchial smooth muscle, reduces release of calcium from intracellular stores, and causes airway smooth muscle relaxation. As with any parasympatholytic drug, potential for tachycardia, thickened mucus, decreased ciliary beat frequency, and decreased mucociliary clearance exists; however, studies in horses have showed no such side effects with doses up to 1200 micrograms. The index of safety is considerably greater than systemically administered atropine. Ipratropium has a slower onset of action than does albuterol, and its actions seem to be confined primarily to the central (larger) airways rather than bronchioles. Studies in horses suggest that pulmonary function begins to improve 15 minutes after administration. Although duration of action has only been verified through

1 hour, clinical evidence suggests that horses experience relief for up to 4 to 6 hours. Although ipratropium may act as a useful adjunct to  $\beta_2$ -agonists for a rescue treatment during exacerbations of RAO, it is not the primary treatment of choice because of its slower onset of action. In horses with adverse responses to  $\beta_2$ -agonists, ipratropium bromide may be preferred.

## Long-Term Control

### *Inhaled Corticosteroids*

Corticosteroids remain the cornerstone of successful treatment for both IAD and RAO. Inhaled corticosteroids have truly revolutionized the treatment of RAO and IAD. Although initial systemic tapered corticosteroid therapy is often necessary with all but very mild IAD, regular inhaled therapy is essential for long-term success in most cases. Inflammation underlies remodeling of the airways with accompanying airway hyperreactivity—or increased twitchiness of the airways—and consequent coughing and expiratory dyspnea. Bronchodilator drugs will help to relieve acute, debilitating bronchospasm, but only consistent anti-inflammatory therapy, in conjunction with avoidance of environmental triggers, will break the cycle of inflammation, airway hyperreactivity, and bronchoconstriction. This philosophy reflects the view that both IAD and RAO are chronic diseases; although they are clinically episodic, the underlying pathology persists even when the disease appears to be quiescent. Hence consistent vigilance in countering airway inflammation is necessary. The most important factor in limiting regular use of inhaled corticosteroids is cost; drugs such as fluticasone and beclomethasone are very expensive.

The antiinflammatory effect of corticosteroids in both RAO and IAD is impressive. Corticosteroids activate glucocorticoid receptors, thus putting into motion a profound inhibition of the arachidonic acid cascade and limiting production of leukotrienes and other inflammatory molecules. Corticosteroids alter the transcription of genes such as inflammatory cytokines and enzymes, directly inhibit inflammatory cells, and decrease goblet cell hyperplasia. Thus they inhibit airway reactivity both by decreasing the mediators available to initiate bronchoconstriction and by preventing the development of airway thickening that geometrically enhances airway hyperreactivity. It has been shown in humans and animals that the efficacy of corticosteroids is limited with high levels of inflammation because transcription factors bind to glucocorticoid receptors, thus blocking the steroid interaction. Response to steroids can vary considerably from horse to horse.

Despite the success of systemic glucocorticoids in limiting airway inflammation, clinicians must aim to limit their use, as their side effects are both considerable and clinically important. Fluticasone propionate (FP) and beclomethasone dipropionate (BDP) are the two most potent, best studied, and most commonly used inhaled corticosteroids in both the horse and in man. They are considered second-generation drugs in that they have greater affinity for the glucocorticoid receptor, and their increased lipophilicity results in longer duration of action and less systemic absorption. In all, this greatly decreases the potential for systemic side effects and allows chronic use of these drugs. Studies in humans have shown that

the longer the use of corticosteroids is delayed both in adults and in children, the worse subsequent lung function becomes. Indeed, regular use of inhaled corticosteroids in humans has been shown to be associated with a greatly reduced risk of death from acute exacerbations of asthma. As there are similarities in the nature of inflammation in horse (RAO) and human (asthma), many concepts in humans that pertain to steroid effects are worth noting.

RAO horses treated with beclomethasone dipropionate have shown both objective and subjective evidence of decreased airway obstruction as well as decreased pulmonary neutrophilia within 24 hours of initiation of therapy. Doses range from 500 micrograms to 1200 micrograms with the hydrofluoroalkane (HFA) formulation, which is approximately half the recommended dose when using the CFC formulation (see Chapter 8.9: "Aerosolized Drug Delivery Devices"). Newer formulations of beclomethasone dipropionate that incorporate hypothalamic-pituitary axis (HPA) as the propellant have more uniform particle size, are more uniformly mixed, and require little to no agitation or waiting before actuation of the inhaler. Although evidence of adrenal/hypopituitary axis (HPA) suppression (i.e., reduced serum cortisol levels) with all doses more than 500 mg exists, this does not appear to pose a risk of chronic HPA suppression or rebound Addisonian crisis. Fluticasone propionate decreases pulmonary neutrophilia, improves pulmonary function, and reduces airway hyperreactivity in RAO-affected horses. Fluticasone propionate is the most potent of the inhaled corticosteroids, has the longest pulmonary residence time, and causes the least adrenal suppression.

The general strategy pursued at the pulmonary clinic at Tufts University School of Veterinary Medicine in Medford, Mass., is to treat in a stepwise manner, starting with a high dose given frequently and gradually reducing therapy until the lowest effective dose can be found. If owners are vigilant in environmental control and are compliant with treatment recommendations, many horses can eventually be treated successfully on an every-other-day basis to prevent recurrences. Some owners have been successful in documenting seasonal exacerbations; in this case we recommend beginning treatment with inhaled corticosteroids—and, occasionally, mast cell inhibitors—at least two weeks before the anticipated allergen season. It is important to remember, however, that unless all stimuli for pulmonary inflammation are removed, the effect of inhaled corticosteroids is transient, and signs will return when the horse is exposed to organic dust and other allergens. Corticosteroids should not be used for quick relief or for rescue therapy because the onset of action is at least 24 hours, and several months of regular use may be necessary for optimal results. With severe inflammation, systemic corticosteroids are usually necessary to achieve breakthrough before inhaled therapy is initiated. Most horses with RAO and IAD will require loading doses for 2 to 4 weeks of systemic steroids before reliance on aerosol medications, although trials to demonstrate the effective preventive dose are lacking.

#### **Mast Cell Inhibitors**

Mast cells are important mediators of inflammation in horses with IAD or RAO, with studies linking mast cells

with airway reactivity, environment, and levels of inflammatory mediators in lavage (BAL) fluid. Sodium cromoglycate has had the most extensive use in horses and is one of the few aerosolized medications that has been examined in the horse. More recently, nedocromil sodium, which has a longer duration of action and appears to be more potent in humans, has been used clinically in horses. These drugs, which most likely work by inhibiting chloride channels, act to stabilize the mast cell membrane, thus blocking degranulation and inhibiting the allergic response at an early stage. Early workers showed that clinical signs were greatly attenuated and that lung function was mildly improved in horses with RAO that were given sodium cromoglycate before challenge. Other studies indicate that disodium cromoglycate can decrease the amount of histamine in mast cells that are seen in the BAL of a subset of horses with IAD. In our hands, disodium cromoglycate and nedocromil sodium appear to be beneficial in some horses with airway hyperreactivity and increased percentages of mast cells. These drugs have a tendency to cause cough, and horses do not like them, perhaps because of a bad taste. Anecdotal evidence suggests that pretreatment with albuterol may attenuate some of the cough response.

The greatest therapeutic effect is seen when this class of drug is given as a long-term therapy and before exposure to allergens—such as before allergy season or before transporting a horse to a new environment. Understandably, this involves less customer satisfaction and consequently poorer compliance with drugs that do not have a visibly dramatic effect, such as the  $\beta_2$ -agonists and even the potent corticosteroids.

#### **Long-Acting $\beta_2$ -Agonists**

Shifting paradigms about nonseptic airway disease in the horse that emphasize inflammation have also led to new approaches to treatment. Initially, this meant that  $\beta_2$ -agonists were relegated strictly to treatment of acute exacerbations or for initial bronchodilation while systemic and inhaled steroids were taking effect. This author tended to counsel against regular use of  $\beta_2$ -agonist drugs except in moderate to severe RAO. However, following the asthma model, the author has begun to treat selected cases of RAO and moderate IAD with long-acting  $\beta_2$ -agonist therapy in addition to inhaled corticosteroids, with the initial impression of enhanced performance and quality of life. It cannot be emphasized enough, however, that regular use of long-acting  $\beta_2$ -agonists must be accompanied with regular use of inhaled corticosteroids.

Although the most obvious and important effect of  $\beta_2$ -agonist agents is bronchodilation, they have a host of other actions that may, in conjunction with antiinflammatory therapy, actually benefit the animal with inflammation-associated airway dysfunction.  $\beta_2$ -agonists have been found—in humans and animals—to inhibit smooth muscle proliferation; increase the force of contraction of the diaphragm and intercostals muscles; act as mild anti-inflammatories by decreasing neutrophil numbers, activity, and ability to release cytokines; protect the epithelium against microorganisms by maintaining cyclic adenosine monophosphate (cAMP) levels; improve mucociliary clearance by increasing ciliary beat frequency; and even enhance surfactant secretion. Studies in asthmatics and



humans with COPD indicate that the addition of long-acting  $\beta_2$ -agonists, in conjunction with corticosteroid therapy, allow a decrease in the corticosteroid dose (which can decrease cost of treatment considerably), decrease frequency and severity of asthma exacerbations, and improve pulmonary function parameters. When long-acting  $\beta_2$ -agonists were used regularly in asthmatic children in the absence of corticosteroid therapy, airway hyperreactivity was not reduced, and symptoms were not adequately controlled.

The most commonly used long-acting  $\beta_2$ -agonists are salmeterol and formoterol, whose basic mechanism of action is the familiar cAMP pathway. Salmeterol has specific binding to the  $\beta_2$ -adrenoreceptor because of its molecular modifications and repeatedly stimulates the receptor. In this way it has a long, concentration-independent duration of action. Its lipophilicity results in slow onset of action; thus it should not be used when rapid bronchodilation is desired. Its duration of action in horses is 6 to 8 hours. Formoterol—although also lipophilic—achieves its long life by being retained as a depot and is thus concentration-dependent. Formoterol has the property of being able to reach the receptor by the aqueous phase and thus has a much more rapid onset of action than salmeterol in humans; formoterol pharmacokinetics have not been studied in horses. Although the duration of action in humans appears to be at least 12 hours, horses appear to experience maximum relief for only 6 hours.

### PATIENT NONRESPONSE TO THERAPY

If response to therapy is poor, detective work to determine why treatment has been unsuccessful is important. It is essential to check the client's technique for using the drug delivery device. Simple issues—such as the use of canisters with no drug, holding the canister upside down, poor mask fit, failure to shake the (metered-dose inhaler) MDI before using chlorofluorocarbon (CFC) formulations, or giving repeated puffs of drug too quickly—may interfere with successful treatment. Occasionally, horses may react to a certain formulation of drug; switching to a different formulation within the same class usually will help. Failure to modify the environment may, in some horses, negate any attempts at drug therapy. Some horses with chronic, severe pathologic processes may be resistant to corticosteroids or may have irreversible changes in the lungs that prevent response to bronchodilators. As noted previously (with short-acting  $\beta_2$ -agonists), lung function testing with albuterol challenge can successfully identify these horses. Finally, lack of response to therapy may be due to underlying infectious disease and may indicate the need for further diagnostics and perhaps an entirely different approach or concomitant antibiotic use.

### SAMPLE TREATMENT REGIMENS

#### Case 1

The typical horse with moderate RAO may have 30% to 70% neutrophils in the BAL fluid, resting airway resistance that is elevated twice to three times normal, and visible

signs of increased breathing effort. This horse would show a 30% to 50% reduction in airway resistance after receiving 450 mcg of albuterol via MDI. This horse would have recommendations for radical environmental modifications and would be treated with a four-week (weeks 1-4) decreasing course of systemic corticosteroids (e.g., prednisolone), with inhaled therapy beginning in the second to third week of treatment (week 3).

#### Week 3

- salmeterol 210  $\mu$ g (10 puffs) twice daily
- fluticasone 2200  $\mu$ g (10 puffs) twice daily

#### Week 4

- salmeterol 210  $\mu$ g (10 puffs) once daily
- fluticasone 2200  $\mu$ g (10 puffs) once daily
- Lung function recheck at end of 4 weeks; if good response:  
salmeterol 210  $\mu$ g once daily  
fluticasone 2200  $\mu$ g every other day

This client should contact the veterinarians monthly, and the horse should have twice-yearly to yearly lung function rechecks to fine-tune inhaled drug therapy and keep the disease in remission. During periods of remission, lung function tests are aimed at measuring baseline airway resistance and airway reactivity. Heightened airway reactivity suggests the need for intensive long-term treatment.

#### Case 2

The horse with IAD is usually younger (2-7 years), although older horses can manifest IAD without heaves. Typical findings include declining performance, cough, and persistent mucoid discharge visible mostly upon endoscopy. Exercise intolerance commonly is observed in horses with IAD, and in these cases, lower airway inflammation is present. Bronchoalveolar lavage reveals elevated neutrophils, mast cells, or eosinophils, and increased airway reactivity to histamine is also present.

#### Examples of Treatments

##### Weeks 1 and 2

- fluticasone 2200  $\mu$ g (10 puffs) twice daily *or* beclomethasone HFA, 1000 mg (5 puffs)
- albuterol 450  $\mu$ g (5 puffs) before steroid inhaler and at least 30 minutes before exercise

##### Week 3

- fluticasone 2200  $\mu$ g (10 puffs) once daily *or* beclomethasone HFA, 1000 mg (5 puffs)
- albuterol 450  $\mu$ g as needed, not to exceed 3 times/week

##### Week 4

- fluticasone 2200  $\mu$ g once daily *or* beclomethasone HFA, 1000 mg (5 puffs)
- albuterol should no longer be necessary
- Rechecking at the end of the week to determine further course of treatment

### Supplemental Readings

Barnes PJ: Clinical outcome of adding long-acting beta-agonists to inhaled corticosteroids. *Respir Med* 2001; 95(Suppl B):S12-S16.

Bjerner L: History and future perspectives of treating asthma as a systemic and small airways disease. *Respir Med* 2001; 95:703-719.

Duvivier DH, Votion D, Vandenput S et al: Aerosol therapy in the equine species. *Vet J* 1997; 154:189-202.

Hoffman AM: Inhaled medications and bronchodilator usage in the horse. *Vet Clin North Am Equine Pract* 1997; 13:519-530.

Rush BR, Raub ES, Rhoads WS et al: Pulmonary function in horses with recurrent airway obstruction after aerosol and parenteral administration of beclomethasone dipropionate and dexamethasone, respectively. *Am J Vet Res* 1998; 59:1039-1043.

## CHAPTER 8.11

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# Immunomodulators in Respiratory Disease Treatment

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M. JULIA B.F. FLAMINIO  
*Ithaca, New York*

The respiratory tract has an efficient mechanical and immunologic defense apparatus for the removal of pathogens and particles that reach the airways from the exterior environment. This mechanism of protection includes adhesive and enzymatic properties of the mucus covering the airways, the mucociliary escalator, the normal bacterial flora that competes with pathogenic agents, and the alveolar and mucosal immune systems. Nevertheless, the function of many of these elements may be impaired under stress, strenuous exercise, long-distance transportation, and infection. Therefore the use of immunomodulators is a rational approach to activate the immune defense for the prevention, attenuation, and early treatment of respiratory disease, before intense cellular damage occurs.

Immunomodulator or biologic response modifier is a substance that enhances or suppresses immune responses. Immunostimulant is an agent that activates immune cells and promotes the release of endogenous immune mediators (cytokines) to assist in the treatment of immunodeficiency disorders, chronic infections, or cancer. In general, activation of the immune response involves the amplification of phagocytosis and intracellular killing of organisms by neutrophils and macrophages, antigen presentation, cytotoxic and antiviral activity of T cells, cytokine release and antibody production, creating resistance to infections or neoplastic conditions. Although immunomodulators generate a nonspecific response to antigen, they exert an effect on the components of both innate and acquired arms of the immune system.

Immunomodulators (Table 8.11-1) function predominantly via activation of macrophages in the liver, spleen, bone marrow, and lungs (pulmonary intravascular macrophages). After the immunotherapeutic agent is phagocy-

tosed, intracellular signaling pathways are activated for gene expression, and the duration of the active status follows the persistence of the product within the macrophages. Therefore multiple doses should give pulses of immune stimulation. The effectiveness of many immunostimulants depends on the animal's own ability to respond with the production of endogenous cytokines, such as interleukin-1 (IL-1), IL-6, tumor necrosis factor (TNF), and interferon (IFN). Systemic reactions after cytokine release vary from mild fever and transient depression to toxic symptoms that include alteration of vascular permeability, hypotension, pulmonary edema, diarrhea, infiltrative/granulomatous cell reaction, and collapse. Paradoxically, these are the same mediators that promote the desirable responses of enhanced immune function. For this reason, immunostimulants must mediate short-term responses.

The selection of a specific immunomodulator should be based on the available information on mechanisms of action and effectiveness investigated by immunologic assays (Box 8.11-1) and clinical trials, in addition to an acceptable degree of safety. The stimulation of the immune response without harmful inflammation and tissue damage is imperative. Effectiveness means regression of the clinical process, prevention of recurrence, and enhancement of overall survival time. In chronic or advanced cases, severe inflammation may overcome the desirable effects of immunomodulators, and best clinical results are obtained when these products are used in the initial phase of disease and in prophylaxis. Nevertheless, the selection of immunomodulators is still challenged by insufficient information on mechanisms of action *in vitro*, lack of clinical trials, deleterious and unknown side effects, lack of response by some individuals, and extra-label use with extreme expectations of efficacy.

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